In September 2010, the ACGME Board of Directors voted to implement work rules which would among other things limit intern shifts to 16 hours effective July 2011. At Jefferson, our leadership team began working on our program’s process and specific plans in attempting to rapidly adapt to the new ACGME mandates even before they were formally adopted. Together with our Chief Residents, Drs. Doug Guggenheim, Dina Halegoua, and Emily Stewart, we planned a retreat for October 22, 2010. It was held at the Union League with assembled residents from all three levels, senior administrators, and faculty that we forged our plan and response. Our goal was not only to comply, but to enhance the educational environment at Jefferson at the same time.

During a preliminary Town Hall Meeting with the Interns—before we even went on retreat—we presented the new ACGME directive for informational purposes including the rationale behind the new rules. Several Interns voiced concerns about preserving education in the new work hours environment. Some asked whether the hours changes would apply to just interns or interns and residents. There was a broad discussion about the affects of a lack of sleep on errors and fatigue and the concern over car crashes post-call. As a result of this meeting we pledged to aim for 16 hour compliance for not just Interns (as the new ACGME work rules mandated), but also for Residents as well (the new rules do permit them to work 24 plus 4 hour shifts).

In considering this revolutionary change, you may have several questions regarding details of our rationale. Over the past decade, a series of studies have emerged indicating that residents’ traditional 24-hr work shifts pose hazards to their patients and to themselves. Elimination of 24-hour shifts has been shown in a randomized trial and other studies to reduce overall error rates. Landrigan et al., showed that houseofficers made substantially more serious errors when they worked shifts of 24 hours or more than when they worked shorter shifts (136 vs. 100 per 1000 patient days, P<0.001). While reassignment of personnel needed to support shorter work hours undoubtedly carries an up front cost (in this circumstance pulling housestaff from the BMT), a decrease in medical errors would more than pay for these costs.

Beyond patient safety, housestaff safety and education are also important. In a series of remarkable conversations I have had with many physicians who trained in the era of no hours limits, I have been amazed by the stories of near car crashes and actual car wrecks that occur driving home post call. Several well conducted studies have validated this important risk. This issue demands bold action to protect the well-being of our residents and unsuspecting motorists.

The imperative for 16 hours comes through the ACGME, I realize, but the imperative should have come from us as leaders in medical education. Whatever the case, we must answer the call and meet not only the letter of the law, but the spirit of the law as well.

Gregory C. Kane MD, FACP, FCCP
Professor of Medicine
Residency Program Director and Vice-Chairman
Interim Chief, Division of Pulmonary and Critical Care
Department of Medicine
We are proud to publish the 11th version of the Medicine Forum. Over the years, the forum has served as an opportunity for medical students and housestaff to pursue scholarly activities alongside learning clinical medicine. This peer-reviewed journal has also served as a platform for rising residents to gain invaluable experience with the editing process as well.

This issue holds several new features. The breath of pieces has been broadened to include public health. Contributors for this journal also collaborated with colleagues from other institutions, including Harvard University and University of Texas MD Anderson Cancer Center. We will be also expanding readership of the Medicine Forum by now being available on Google Scholar.

In light of the new ACGME work-hour regulations for housestaff, the changing trends in medical training are becoming more apparent. We see this edition as a kick off to expanding the training of clinicians as researchers and contributors to the wealth of knowledge in medicine. We aim to strengthen this journal in future years to keep on par with the renewed focus on scholarly activity. Jefferson has always prided itself in developing strong and well-balanced clinicians. We hope you enjoy the articles and artwork from our community.

Regards,

Sameh Gaballa, MD, Toshimasa Okabe, MD, and Tina Shah, MD
Executive Editors

Gregory C. Kane, MD
Matthew T. Smith, MD
Marion T. DiFiglia, MD
Alan H. Wang, MD

Yaa Oppong, MD
Andrew Lerner, MD
Eve Merrill, MD
Bryan LeBude, MD
Rina Shah, MD
Sean O'donnell, MD
Katie Osley, MD

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photograph by
Douglas Guggenheim, MD
Disruptive Innovation
Peregrine Dalziel, MBBS and Tina Shah, MD

Introduction

“Disruptive innovation” (DI) has recently been heralded as a tool to mitigate out of control health care spending in the United States, however few doctors are familiar with the concept. Overall, there is a tendency in medical culture to regard changes to established treatment and management models with some reticence, increasing the difficulty for reform. In this article we will introduce readers to the concept of DI as a means to reduce costs in the American health sector. We will illustrate current uses of DI in health care, using the particular example of the expanding role of nurse practitioners (NPs). It is not our intention to debate the virtue of NPs per se, but we will examine arguments for and against the development of the NP role that illustrate traditional barriers in health care to DI adoption, and some of its potential synergies.

The Need to Cut Costs

Health care is clearly in need of reform in the United States. Health care sector spending is 3 times the national defense budget. Health care cost inflation consistently outstrips the average increase of the Consumer Price Index and constitutes 17% of the GDP; nearly 1 out of 5 dollars spent in the US is spent on healthcare. Furthermore, 62% of bankruptcies in the US have medical debt as a major contributor. Unfortunately, pressures that increase costs are getting worse: our population is aging, chronic disease and comorbidities are increasing, the primary care workforce is shrinking, and there has been an increase in high-tech services and government commitment to universal health coverage. Doctors are in an unenviable position of having to devote more time to increasingly complex patients with complex treatment options, while having to also meet the demand for higher quality services. Clearly the incumbent medical model will need to change.

Allowing DIs in health care delivery may be a method of achieving these seemingly opposed goals of providing greater access to health care whilst controlling costs.

Disruptive Innovation

A DI is one that displaces a “status quo” technology or process by offering a reliable, cheaper, though generally lower quality alternative. This innovation is adequate for the average consumer’s needs and can be used by less skilled or trained users. Figure 1 illustrates the key features of DIs. Initial innovation in an industry is targeted toward the high-end/advanced users who fund its development and are prepared to pay higher prices for better quality. This incremental “sustaining” innovation continues with improvements on the existing technology and provides higher and higher quality and performance with more “bells and whistles”. Eventually, these added features become beyond what is necessary for the average purchaser. On a greater scale, institutions that are built upon the sustaining innovation are so invested in its continuation that it is impossible to change their business model to then target the average consumer.

The DI enters the market providing a lower functional or quality level product/process, but this satisfies the needs of less demanding consumers. The lower price makes it more affordable and opens the market to previously excluded users. Eventually, the new product becomes widespread and subsequent improvements in quality and performance make it good enough to satisfy even high-end consumers [dotted line]. It may then completely supplant the old technology.

Examples of DI abound in the non-medical realm. Mainframe computers had their market dominance interrupted by smaller, cheaper, though less powerful, personal computers. Telegraph operators were disrupted by the telephone. Compact discs overtook LPs, followed by MP3s that now provide a smaller, cheaper, and more convenient alternative to CDs with a loss of sound quality that is accepted. Internet calling services and mobile phones have made traditional domestic telephone lines nearly obsolete for many users in developed countries. DI has been less forthcoming in redefining the health industry. There have been some notable examples of cost-saving DIs, such as coronary artery stenting which disrupted cardiac surgery, or the development of hemoglobin A1C testing and hand-held glucose monitors that enabled diabetes management by non-specialists. Use of bedside emergency ultrasound also disrupted the need for expensive computed tomography scans in emergent settings. Overall however, the capacity for disruptive change in health care has been stifled by heavy industry regulation and lobbying by specialist interest groups.

Disruptive Innovation Allows Transmission of Routine Tasks to “Value-Added” Processes

Hwang & Christensen explain 3 basic overarching models for service delivery:

1. The “solution shop” model. Highly trained professionals provide “bespoke” care using their training, experience and intuition for individualized solutions to problems. The value of this model is brought by the professional’s skill and experience. Examples include consulting firms, some law firms, engineering and design firms.

2. The “value added” model. Resources and labor are used to create an essentially uniform, re-creatable product or service on a larger scale. Examples include manufactured
goods, department stores, and most service businesses. Here the value lies in the process and the ability to faithfully reproduce the product at a lower cost.

3. The facilitated network. Consumers largely solve their own problems through the provision of an interface with other consumers, for example buying goods on eBay, or finding a partner on a dating website.

Hwang and Christensen argue that medical training and practice has largely developed based on the “solution shop” model, where practitioners are highly trained to deal with complex healthcare situations. Much of this skill set is unnecessary to meet the needs of most health consumers, who present with simple complaints.

A by product of the “solution shop” approach is the development of evidence-based and process-oriented solutions which are used by less trained providers to provide quality care, thus transitioning to a “value added” model. Under this DI, specialists are disrupted by generalists, physicians by other clinical staff, and ultimately trained staff by patients themselves (e.g. home glucose and blood pressure monitoring).

A Major Barrier to Disruptive Innovation

Physician led healthcare is the paradigm that is taught in medical schools, granted by virtue of considerable knowledge and practical experience from university and residency training. Notions of health system performance and evidence-based cost containment methods are not considered core requirements of physician activities. If physicians, the governing bodies that represent them, and the supervisory groups who are responsible, make up want to remain as a strong force in medicine, widespread change will need to occur, likely at the medical student and resident level. Going from the teachings of history, we should learn to adapt DI such as NPs, in order to avoid being the obsolete mainframe computer or LP. Others echo such opinion. Dr. Thomas Lee, network president for Partners Health Care system in Boston, MA states it well: “A shift to value-oriented, performance-driven health care requires doctors to adapt or even reject some ways of working that are embedded in medicine’s past...they have no choice. Defending the status quo is no longer a viable strategy, even in the near term.”

Nurse Practitioners as a Disruptive Innovation

The use of “mid level care providers” such as NPs is not a novel concept. As policy makers are undertaking what will be the largest overhaul of the health sector in recent history, use of mid-level providers arouse considerable interest. NPs are a good illustration of DI for several reasons: they are not a new concept, NPs are already involved in primary care and in role substitution in hospitals and nurses are the largest group of healthcare professionals in the US. Evidence suggests that NPs provide an equivalent quality of care compared to physicians in a number of settings. The increasing autonomy of NPs as a DI has raised significant opposition from the “sustainers,” the incumbent care providers.

We will briefly outline the key features of the NP role as well as some the pros and cons of its utilization in the health system.

Background and Current Role of Nurse Practitioners

The NP role was created in 1965, as a collaborative position with physicians. NPs are a type of “advanced practice nurse,” alongside nurse-midwives and nurse anesthetists. NPs are required to have a master’s degree in nursing with certification from a professional nursing organization. There are about 158,348 practicing NPs.

NPs differ from physicians in several ways. Fiscally, NP salaries are lower in comparison to primary care physicians. Scope of practice varies across state lines but generally allows independent prescribing authority for non-schedule IV drugs and some autonomy for delivery of health service. In Pennsylvania where NP autonomy is high, prescribing authority is almost equivalent to that of physicians: NPs can prescribe all levels of DEA controlled substances but are limited to writing a 30 day supply for schedule IV drugs.

Pennsylvania law allows NPs to work in a range of areas including surgical practices, inpatient wards, primary care offices, and retail clinics. NPs can function independently, provided that they have a predetermined plan for emergency services, and immediate availability of a licensed physician directly or via radio, telephone or telecommunications. In addition, a doctor must be available for referrals and review of standards of medical practice on a regular basis. NP organizations are currently lobbying to remove the requirement of “supervision” by physicians.

Nurse Practitioners Could Be A Successful Disruptive Innovation

NPs offer a number of appealing prospects to policy makers and private insurers as a complement to physicians that make them an example of a successful DI.

NPs typically receive lower reimbursements from insurance companies and demand lower incomes. For instance, Medicare rebates are set at 85% of the physician fee for an equivalent service. A recent RAND study conducted in Massachusetts highlighted that costs of NPs were on average 35% lower than those of physicians. Under conservative predictions where NPs constitute less than 10% of the workforce, and autonomously treat 6 core conditions, costs were reduced by 4.8 billion dollars. NPs have a median salary of $85,200 and upper limit of $113,000, compared to a range of $121,068 – $155,294 for primary care doctors. If similar, high quality service can be
provided, utilizing these physician extenders can help control national health care costs.

NPs already provide a range of services that are traditionally given by physicians and are utilized in a number of medical settings with equivalent results. New technologies and the development of clinical algorithms mean that NPs can fully deal with a variety of routine clinical scenarios. For instance, current diagnostic kits for Group A Streptococcus pharyngitis allow for easy diagnosis, and evidence-based treatment protocols almost “automate” management of uncomplicated pharyngitis. Decision rules based on diagnostic scoring systems such as the Ottawa ankle rules or Wells criterion for deep venous thrombosis promise to facilitate more complex decision-making by NPs.

Much of the policy debate between physician and NP groups revolves around establishing authority of ultimate patient management and gaining or maintaining professional autonomy. In this context NPs and primary care physicians are perceived as “substitutes” in competition with one another. Proponents for NPs highlight that their different clinical background improved care through patient focused, team approaches. Anecdotal evidence and some research even suggests that physicians working with NPs report greater job satisfaction. Under this model, physicians and NPs do not compete but tackle tasks more suited to their training and experience; doctors work on “solution shop” problems that fall outside the realm of strict protocolized care and NPs perform in a “value added” task role.

This emphasis on multi-disciplinarianism is something that few would consider unhealthy in medical care, even though it challenges some older physicians’ notions of themselves as “lone healers.”

Some believe that the growing role of NPs will not be effective. One major argument against expanding NP roles is the delivery of lower quality health care. The American Academy of Family Physicians (AAFP) is one group that opposes giving NPs more autonomy. They argue that family doctor training requires 4 years of medical school and 3 years of family practice residency with training in 6 major areas, while NP programs require only 2 additional years of classroom and clinical training. While some studies have shown that mid-level providers perform equally to physicians with algorithmic approaches to common primary care conditions, there is a concern that NPs may be ill equipped to deal with complicated patients. Former AAFP president Warren A. Jones stated in a 2002 editorial, “This may be appropriate training for an NP, but it certainly is not adequate to prepare an individual to face the diagnostic complexities that even the least complicated of patients bring to a family physician.”

Current policy recommendations are also criticized as having flaws that will lower the quality of primary care. The 2010 Institute of Medicine report, “The Future of Nursing: Leading Change, Advancing Health” advocates eliminating legislative barriers to practicing medicine for NPs to meet the demand for primary care providers. However, there is no mention in the report about how to maintain NP competencies or ensure patient safety. Physician providers have established regulatory bodies and are part of data networks that can be and are utilized for quality improvement. If there are no policies set in place to ensure NP education for the latest standard of care and for outcomes research, the quality of primary care as a whole may decrease, worsening the American health sector.

NPs as independent providers in primary care could have other ramifications. For instance, there may be a prolonged time-to-diagnosis, due to limited NP clinical experience and having to go through additional visits before seeing the doctor. Instituting health services that control costs at the primary care level but cause lag-times to diagnosis could increase utilization of expensive technologies later on, diminishing perceived savings. With the filling of the primary care gap by less expensive NPs, market forces could lower reimbursements to family physicians, further decreasing the incentive for medical school graduates to enter primary care. A lack of physicians in primary care may undermine the whole model of mid-level providers by quality issues.

On an ethical level, the emerging use of this DI could be a strike against libertarianism. The right to choose is a value embodied in the American psyche. If insurers shift to reimburse only primary care given by NPs, patient autonomy and their right to seek medical care from a doctor may be lost here.
Conclusion

DIs such as the NP role in primary care may be a positive force for change in this environment and will help catalyze a shift away from physicians having to provide “value-added” tasks that can be performed by personnel with narrower training. This model may in turn encourage DIs elsewhere in the system, shifting care from specialist to generalist for instance. Significant efforts need to be made on the part of policy makers and administration to ensure that utilization of such change enhances rather than compromises patient care. Necessary monitoring of quality and adequate supports for appropriate education will be needed. Well-constructed policies and strong leadership in the face of predictable opposition will be required. We also argue though that combined with any specific policy changes for a particular DI, there must be considerable effort to reform current hegemonic thinking in medical culture. We must educate new doctors to embrace, rather than reject such changes—especially where patient and health service benefit is demonstrated.

References


5. Figure 1. Slide courtesy of J. Hwang by personal communication.
**Ventilator Management for the Non-Intensivist**

David R. Manoff, MD and Christine Feldmeier, MSIV

The management of the mechanical ventilator is one of the most complex and dynamic, yet ubiquitous issues to face the critical care physician. As we as a medical community have become more advanced, so too, have our ventilators, with new modes and variables having been added beyond more traditional modes like Assist Control and Intermittent Mandatory Ventilation. This article is designed to give a very basic understanding of what the individual ventilatory modes do and how they are set. It is in no way meant to be a replacement for either a medical intensivist or a respiratory therapist.

**The Decision to Intubate**

On a fundamental level, the decision to intubate a patient and to assume control of their breathing is a clinical judgment. However, there are several broad reasons why one may decide to intubate the patient. The first of these is to support the airway. This takes into account both physical reasons, such as airway compromise but it also includes those situations in which there is an anticipated need to control the airway, whether due to a significantly impaired mental status or because of high potential for needing to establish an airway when it may be difficult to do so.1 The second set of circumstances under which intubation may be needed is due to a pulmonary process, such as inadequate oxygenation or ventilation. This includes having failed non-invasive techniques such as BiPAP or CPAP and also during a code situation, though we recognize that intubation is not strictly indicated in current ACLS guidelines1. The third major indication for intubation is for other reasons not necessarily cardiopulmonary but rather as an adjunct. This is to say that intubation and mechanical ventilation may need to be used in other situations, such as hyperventilation for increased intracranial pressure.1

**Initial Ventilation**

Once the decision is made to intubate and place the patient on a ventilator, the initial ventilator mode is almost always Assist Control and a knowledge of this mode should enable the practitioner to treat the ventilated patient in the first period of time after intubation and until more experienced providers can lend their expertise.

**Assist Control Ventilation**

Assist Control (AC) is essentially a derivative of Controlled Mechanical Ventilation (CMV), which was one of the first modes of mechanical ventilation and which gave a predetermined tidal volume at a set rate regardless of the patient’s attempts at spontaneous respiration.2 In AC mode, the patient receives the preset tidal volume regardless of whether the breath is a controlled breath or if it is patient initiated. In this mode, the ventilator does the overwhelming majority of the work of breathing though it remains possible to have “breath stacking,” in which the patient triggers a breath prior to completing an exhalation of a prior breath.2 In those patients who have no spontaneous respiration, such as those who are receiving paralytics or heavy sedation, AC essentially is a mimic of CMV and the patient will only receive the set number of breaths at the set tidal volume.

While Assist Control Ventilation has been in use for several decades, perhaps the greatest change to how it is used occurred with the series of Acute Respiratory Distress Syndrome Network (ARDSnet) trials. While these trials continue, a multicenter trial in the late 1990s found that low tidal volumes, initially set at 6 cc/kg and titrated based on plateau pressures, had a mortality benefit when compared with conventional, higher tidal volume ventilation.3 Of note, in this study, the pH of the patients was closely followed and corrected with bicarbonate infusions or ventilatory rate increases if needed for even mild acidosis.3

**Pressure Control Ventilation**

Similar to AC, and listed on some ventilators as “Pressure Assist Control,” this mode is also either patient or time triggered but is pressure cycled, rather than volume cycled. In pressure control, there is a set rate over which the patient may breathe but each breath is delivered to a set inspiratory pressure, rather than to a set tidal volume. This mode has its primary use in those with poorly compliant lungs and in those in whom there is a significant concern for barotrauma. Unfortunately, it is more uncomfortable for the patient than the volume cycled assist control and may require more sedation to use.

**Initial Ventilator Settings**

While the settings used when initially placing a patient on the ventilator may vary based on the individual, there are several broad guidelines which can be used with subsequent titration based on the patient’s needs. In the average patient, either AC or the Synchronized Intermittent Mandatory Ventilation (SIMV) mode, described below, can be used though AC is usually preferred.2, 3 In order to maximize oxygenation, an FiO2 of 1 (100% oxygen) is used, though this is titrated rapidly based on PaO2. Also in order to optimize oxygenation, positive end expiratory pressure (PEEP) is usually set at 5 cm H2O in order to prevent alveolar collapse.2 While earlier studies and recommendations were for the initial tidal volume to be at 8-10 cc/kg of ideal body weight, after the ARDSnet trial discussed above, it is now more common to have initial tidal volumes at 6-8 cc/kg of ideal body weight.2, 3
Subsequent to these initial settings, further adjustments can be made based on the patient’s oxygenation and acid-base needs. Using conventional modes of ventilation such as AC, a patient’s oxygenation can be augmented by raising F\textsubscript{O2}, if possible, or increasing the PEEP, though an increase in PEEP also comes with an increased danger of barotrauma. The respiratory rate and tidal volume can be manipulated based on the P\textsubscript{a}CO\textsubscript{2} and pH, with an increase in rate or tidal volume yielding a lower P\textsubscript{a}CO\textsubscript{2} and higher pH.\textsuperscript{1}

**Weaning**

Prior to any discussion of weaning on the mechanical ventilator, it should be noted that weaning is not a mode or set of modes on the ventilator, but rather a process involving daily determination of the patient’s ability to do more of the work of breathing. This is in contrast to liberating the patient from the ventilator, which is a more rapid process and one which is used for those patients who have been mechanically ventilated for short periods.

**Synchronized Intermittent Mandatory Ventilation (SIMV)**

A derivative of Assist Control, SIMV is a mode of ventilation initially designed to be used in patients in anticipation of discontinuing mechanical ventilation. It is a mode which, at its base setting, will deliver a set tidal volume at a set rate, similar to assist control. It differs from assist control in that it allows the patient to breathe assisted breaths in between the controlled breaths. These assisted breaths can be with or without pressure support behind them. In theory, this mode works by resting respiratory muscles during the controlled breaths while working these same muscles during spontaneous breaths.\textsuperscript{4} Thus, a conventional weaning procedure using SIMV would involve a gradual decrease in the control rate while allowing more spontaneous breathing with, or without pressure support.

Unfortunately, it has been demonstrated in multiple studies that, in fact, rest of the respiratory muscles does not occur during the mandatory breaths. One study found that the brain’s respiratory center does not anticipate the mandatory breaths from the ventilator, actually increasing the potential for fatigue.\textsuperscript{1} When compared against gradual Pressure Support trials or T-piece trials SIMV was actually found to be associated with significant increases in the time required for a successful wean.\textsuperscript{3}

It should also be noted that, in spite of the paucity of evidence favoring SIMV as a weaning mode, this mode of ventilation continues to see some use as a primary form of ventilation. When compared to Assist Control, a multi-center observational study by Ortiz et al. failed to demonstrate any advantage to the use of SIMV over AC as a primary mode for mechanical ventilation.\textsuperscript{5}

**Pressure Support Ventilation (PSV)**

Pressure Support is a form of mechanical ventilation in which all breaths are patient-triggered but each triggered breath is augmented by a set level of inspiratory pressure. Perhaps the best analogy is to equate PSV to an invasive BiPAP in which the pressure support set is equivalent to the inspiratory airway pressure on the BiPAP while the PEEP is equivalent to the expiratory airway pressure. Initially, the patient is started at a high degree of support wherein there is a disproportionate degree of work by the ventilator relative to patient effort.\textsuperscript{4} In a weaning protocol using this mode, the degree of support is decreased as tolerated by the patient from nearly full support to a low pressure support of approximately 6-10 cm H\textsubscript{2}O, at which point the patient could theoretically be extubated.\textsuperscript{1,7}

**Spontaneous Breathing Trials (SBTs)**

Of the different modalities used to wean a patient from the ventilator, the spontaneous breathing trial is the oldest.\textsuperscript{1} It usually is done either by CPAP, i.e., PEEP alone, or by a low pressure support setting.\textsuperscript{4} If no pressure support is to be used, it is possible to set the ventilator to allow CPAP only, but it is also possible to attempt spontaneous breathing via either a T-piece or via Tube Compensation (TC) on the ventilator itself, which theoretically allows only enough support by the ventilator to overcome the increased resistance of having an endotracheal tube in place.\textsuperscript{1}

**Success or Failure of Weaning Trials**

As stated previously, weaning is a process, not a single mode of ventilation. The need to recognize probable success or failure is inherent in this and much study has gone into predicting the outcome of weaning. Perhaps the most common of the assessments for success at weaning is the Rapid Shallow Breathing Index (RSBI) or Tobin Index. Classically, this index was calculated by placing the ventilated patient on a T-piece and then measuring their tidal volumes on a spirometer.\textsuperscript{7} When calculated as respiratory rate in breaths per minute divided by tidal volume expressed as liters, a score of at least 105 is considered to be highly sensitive and specific for success at weaning from the ventilator.\textsuperscript{7} While this is the most commonly used indicator of potential success in the ICU setting, it also should be noted that there have been several challenges to modifications of the RSBI. Namely, the use of PEEP and low pressure support have both been shown to lower the RSBI, making their recommendation that this score only be considered if it is calculated in the traditional manner with a T-piece.\textsuperscript{5}
Conversely, it is also necessary to be able to recognize when a weaning trial has failed. Broadly, any significant change in vital signs for a sustained period of time should be considered to be a trial failure, as should any agitation, anxiety, or diaphoresis in a patient in whom these findings have not been seen before.

**Rescue Modes**

While the initial ARDSnet trials were done on Assist Control using low tidal volume ventilation, it should be noted that in the subsequent years, both new modes and re-emergent old ones have been increasingly used in those patients who are difficult to oxygenate or ventilate. These should not be used as the initial ventilatory mode in any patient but serve an important role in the patient with ARDS and should be considered if more conventional forms of ventilation fail.

**Airway Pressure Release Ventilation (APRV)**

Also referred to by multiple proprietary names including BiLevel and DuoPAP, this mode, first described in 1987, is essentially a mode in which the patient is ventilated between two set ventilatory pressures ($P_{hi}$ and $P_{low}$) for set time periods ($T_{hi}$ and $T_{low}$). For this mode, the change between the high and low pressures allows for ventilation while breathing at the high pressure allows for minimizing recruitment of alveoli, and therefore maximizing oxygenation. In spite of this, some spontaneous breathing at the high pressure is required in order to allow adequate oxygenation. Initially, the majority of time is spent at the high pressure and the time at the lower pressure is limited to 0.6-0.8 seconds. The high pressure is set at the lower of either the plateau pressure measured on a conventional mode of ventilation or 30 cm H$_2$O in order to minimize barotrauma. On the other hand, the low pressure is usually set at 0 cm H$_2$O.

To treat hypoxia using this mode, either the $F_{O2}$ or the pressure and time at the high pressure setting must be adjusted. Conversely, in order to treat hypercapnea, which is somewhat expected using this mode, the frequency of respiration will be increased. This does have the effect of concomitantly decreasing $T_{hi}$. Once the patient has been stabilized on this mode and it is time to perform a wean, while the patient can be transitioned to a more conventional mode of ventilation, it is also possible to wean via APRV. In this setting, the $P_{hi}$ is gradually lowered while the $T_{hi}$ is increased so that once the $P_{hi}$ is sufficiently lowered, say to 10-15 cm H$_2$O, the patient can be transitioned to CPAP.

While the advantages of this ventilator mode include that it can be done with the same ventilator and the same equipment, and that its very design requires some effort on the part of the patient, the evidence to support its use has been variable. One single center trial of 58 patients comparing APRV against SIMV after initial use of AC found that initial peak inspiratory pressures were lower for APRV but that oxygenation, hemodynamic indices, and 30-day mortality were identical. Conversely, a small single-center trial evaluating for atelectasis found that APRV was superior to PSV based on CT scans of the thorax.

While APRV has yet to be conclusively shown to be of benefit, it should be considered in the patient with ARDS with high ventilatory pressures and in whom oxygenation is proving difficult with traditional ventilatory techniques.

**High Frequency Oscillatory Ventilation (HFOV)**

High frequency oscillatory ventilation is a type of mechanical ventilation in which small tidal volumes, usually 1-4 cc/kg, are delivered at a high frequency, ranging from 3-15 breaths per second. In theory, this is designed to maximize oxygenation while minimizing alveolar over-distention and derecruitment. The early data regarding this technique is conflicting and it has several disadvantages, most notably the need to obtain a specialized ventilator and the fact that often times, the use of paralytics is necessary in order to ensure patient-ventilator synchrony.

One initial trial of 148 patients with ARDS found that at 30 days, there was no statistically significant difference in ventilator-free survival between the group assigned to receive HFOV and those who received conventional ventilation. Of note, this initial trial involving HFOV was performed prior to the 2000 ARDSNet trial’s publication and allowed permissive hypercapnea to a pH of 7.15, but also did not use low tidal volume ventilation universally in their conventionally ventilated patients.

In contrast to the study above, in 2010, a meta-analysis was released by Sudet al., based on eight trials involving a total of 431 pediatric and adult patients comparing HFOV to conventional ventilation. In this meta-analysis, HFOV was shown to reduce 30-day mortality, as well as reducing risk of treatment failure, but without a significant difference in the rates of barotrauma, obstruction of the endotracheal tube, or of hypotension.

Though studies are ongoing, and in spite of the potential of this mode of ventilation, because of the need for specialized equipment and training, we would only advocate the use of this technique while the patient is under the care of a medical intensivist.

**Extubating**

Once the patient has passed a spontaneous breathing trial and has ensured sufficient respiratory muscle strength and ability to both oxygenate and ventilate, other factors which would require continued intubation need to be assessed. The patient must be able to protect their airway, both physiologically, and in terms of mental status, and also be able to manage secretions. If a patient requires frequent suctioning at more than every two hour intervals, it is possible that they may not yet be ready for extubation.

If a patient is deemed ready for extubation, it should be noted that previous studies have found extubation failure rates, i.e.
re-intubation within 48-72 hours of extubation, of 5-20%. Nonetheless, delays in extubation have also been associated with increased rates of ventilator associated pneumonias, duration of ICU stay, and overall increased in-hospital mortality.13

Conclusions

While the decision to intubate a patient and assume control of their breathing should never be taken lightly, it is often necessary in the critically-ill patient. Once the patient has been intubated, we recommend initial use of Assist Control Ventilation using the setting outlined above. Then, with the guidance of the intensivist and the respiratory therapist, the patient’s ventilator settings can be tailored to meet the patient’s needs. It is our hope that this article provides a bit of guidance on how to transition your patient from that initial period to liberation or weaning from the ventilator to extubation.

Acknowledgments

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References


"Villa on a Hill", photograph by Paurush Shah, MD
Thrombotic Thrombocytopenic Purpura: A Review of the Disease Entity, its Clinical and Laboratory Features, and Management Strategies

Rosemarie Beckford, MD and Gunjan Shah, MD

Case 1

The patient is a 47-year-old female with a history of coronary artery disease, hypertension, asthma, diabetes and obstructive sleep apnea who presented to an outside hospital with shortness of breath and lethargy. The patient was found to be in diabetic ketoacidosis, which was treated with an insulin drip. She also had a platelet count of 8 x 10^9/L on initial laboratory studies. She was presumed to have immune thrombocytopenic purpura (ITP) and treated with five days of intravenous immunoglobulin (IVIG) without improvement. She was transferred to Thomas Jefferson University Hospital for further management.

Initial vital signs included a temperature of 100.1 degrees Fahrenheit, pulse of 101 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 107/45 mmHg and oxygen saturation of 100% on room air. On physical exam, she was lethargic and not oriented. She had pupils that were equally round and reactive to light; her extraocular muscles were intact. She had no lymphadenopathy. Her cardiac exam revealed a regular rate and rhythm with no murmurs. Her extremities demonstrated purpuric lesions throughout, but were non-tender, non-distended, with normal bowel sounds. Her abdomen was soft, non-tender, non-distended, with normal bowel sounds. Her abdomen had no cracks in her lung fields. Her abdomen was soft, non-tender, non-distended, with normal bowel sounds. Her abdomen had no crackles in her lung fields. Her abdomen was soft, non-tender, non-distended, with normal bowel sounds. Her abdomen had no crackles in her lung fields.

As there was a concern for thrombotic thrombocytopenic purpura (TTP), a peripheral blood smear was evaluated and found to have schistocytes. There was also evidence for microangiopathic hemolytic anemia (MAHA) demonstrated by a lactate dehydrogenase (LDH) of 1451 IU/L (normal 100-200 IU/L) and a haptoglobin of 31 mg/dL (normal 16-200 mg/dL). Given the presence of a low grade fever, MAHA, thrombocytopenia, and mental status change, a diagnosis of TTP was presumed.

The patient required intubation for airway protection. An apheresis catheter was placed, and urgent plasmapheresis was started. Her course was complicated by transient low blood pressures which were treated with norepinephrine infusion for two days. Her course was complicated by a spontaneous retroperitoneal hematoma, which accounted for a further decrease in her hemoglobin and required transfusion of packed red blood cells. The patient was also treated for a multifocal pneumonia and Clostridium difficile diarrhea. She also had acute renal failure which was thought to be acute tubular necrosis secondary to her transient hypotension rather than the TTP.

The patient received 3 weeks of daily plasmapheresis and high dose intravenous methylprednisolone and then oral prednisone, with monitoring of her LDH and haptoglobin. She also received one dose of rituximab during her hospital stay. Her ADAMTS13 (an acronym for a disintegrin and metalloproteinase with thrombospondin-1-like domains) activity level was < 5% (normal more than 67%) and ADAMTS13 inhibitor level was > 8.0 Inhibitor Units (normal < =0.4 Inhibitor Units). On discharge, her LDH was 218 IU/L, hemoglobin 10.4 g/dL, and platelet count 139 x10^9/L.

Case 2

The patient is a 61-year-old female with a history of systemic lupus erythematosus, a transient ischemic attack, and human papilloma virus. Additionally, she had a prior episode of TTP six years ago that presented with symptoms of confusion and purpura. She was treated at that time with plasmapheresis. She presented to an outside hospital with confusion and numbness of the right neck that radiated down the right arm and leg. The patient could speak but could not respond appropriately to questions. She was transferred to Thomas Jefferson University Hospital for further management.

Initial vital signs included a temperature of 99.3 degrees Fahrenheit, pulse of 105 beats per min, respiration of 18 breaths per min, pulse oximetry 98% on room air, and blood pressure 159/85 mmHg. On physical exam, she was alert and oriented to person, place, and time. She had pupils that were equally round and reactive to light; her extraocular muscles were intact. She had no lymphadenopathy. Her cardiac exam had regular rate and rhythm with no murmurs. She had no crackles in her lung fields. Her abdomen was soft, non-tender, non-distended, with normal bowel sounds. Her extremities had no edema, but did have petechiae on the arms and legs. She had recovered sensation and strength of her right side.

Laboratory studies showed a hemoglobin of 6.5 g/dL, white blood cell count of 13.3 x10^9/L, and platelet count of 65 x10^9/L. Her creatinine was 0.9 mg/dL.

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discharge, ADAMTS13 activity level had risen to 34%, while the ADAMTS13 inhibitor level continued to be <0.4 Inhibitor Units. The hematologist consulted on this case believed that the patient had a congenital form of TTP demonstrated by an overlap syndrome with low activity levels in the absence of inhibitors.

**Discussion**

Thrombotic thrombocytopenic purpura (TTP) is a rare condition on the spectrum of disorders termed thrombotic microangiopathies (TMA). It is characterized by the presence of acquired microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fluctuating neurological symptoms, renal dysfunction and fever. TTP can be seen at any age though predominately it presents in the 4th decade of life. It is estimated that the annual incidence of TTP in the United States is 4 to 11 cases per a million individuals. Additionally, the incidence of TTP in women is greater than men by approximately 2 to 2.5 times, and black to non-blacks at approximately 3 to 5 times greater. Though typical of TTP, the constellation of findings that constitute the classical pentad can also be seen in other TMAs. These include hemolytic uremic syndrome or MAHA associated with other causes including metastatic cancer, organ transplantation, and connective tissue diseases. Furthermore, not all features of the pentad need be present to diagnose TTP. Treatment initiation, particularly plasma exchange, can significantly decrease the mortality of the disorder and is often initiated prior to confirming the diagnosis. The purpose of this paper is to raise the index of suspicion for a diagnosis of TTP in cases of thrombocytopenia and to expedite prompt implementation of effective therapy.

**Categories of TTP**

TTP can be classified into subcategories, namely idiopathic TTP and familial TTP. Idiopathic TTP is the predominant form of TTP. It can be further subdivided into acute TTP (occurring without a known precipitant and once treated typically resolves within 4 weeks and without relapses), and relapsing TTP (wherein episodes of TTP respond to therapy with relapses occurring as early as 4 weeks after therapy). Familial TTP carries a poor prognosis and is usually transmitted via an autosomal recessive pattern of inheritance.

**Pathophysiology**

The hallmark feature of TTP is the presence of microvascular thrombi in arterioles and capillaries throughout the body. These microvascular thrombi consist of platelets with a small amount of fibrin surrounded by proliferative endothelial cells. This contrasts to the typical thrombi noted in HUS which are composed of mostly fibrin with few platelets. In addition, TTP thrombi are more disseminated than those of HUS, and are found in the heart, pancreas, kidneys, adrenal glands and brain. Conversely, HUS thrombi typically affects the kidneys predominantly. Other organs including the lungs, skeletal muscles, liver and gastrointestinal tract may be affected by TTP thrombi albeit to a lesser extent and may contribute to the constellation of symptoms that an individual patient may express. The hemolytic anemia seen in TTP results from alterations in microcirculation, in addition to the passage of red blood cells through partially occluded vessels. The peripheral destruction of platelets and their aggregation into microthrombi, as well as disruption of circulating red blood cells, leads to the presence of schistocytes and the paucity of platelets characteristic of the blood smear in TTP.

**Von Willebrand factor and ADAMTS13**

Von Willebrand factor (vWF) is found in the platelet rich thrombi of TTP patients. It is a large, multimeric plasma glycoprotein that mediates platelet adhesion and subsequent thrombus formation at areas of vascular damage. It is synthesized in the endothelium and megakaryocytes and secreted into plasma as large multimers or "strings". These multimers are subsequently cleaved by a metalloproteinase enzyme to prevent their entrance into or persistence in plasma. This metalloproteinase is called ADAMTS13. Once cleaved, the adhesion of platelets to monomers of vWF does not occur in the absence of vascular damage. In patients with a deficiency of ADAMTS13 or impaired activity of this enzyme, these large multimers of vWF are not cleaved. In this form, they may act as the nidus for platelet aggregation and subsequent thrombi formation. In patients with familial thrombotic thrombocytopenic purpura, unusually large multimers of vWF can be found in the plasma. Their plasma ADAMTS 13 activity is undetectable to barely detectable. For patients with idiopathic TTP, plasma levels of ADAMTS 13 are barely detectable during the episode but normalize following recovery.

Remuzzi et al. showed that during the acute phase of TTP a complete deficiency of ADAMTS13 activity had a sensitivity of 92% and a specificity of 44%. For patients in remission, complete deficiency of ADAMTS13 activity had a sensitivity of 41% and a specificity of 82% for diagnosis of TTP. In patients with antibodies against ADAMTS13, the specificity of diagnosing TTP was 100%. Further studies have shown that survivors of an acute episode of acquired TTP with severely reduced levels of ADAMTS13 or with anti-ADAMTS13 antibodies during remission have an approximately three-fold greater likelihood of developing another episode of TTP than patients with higher protease activity and no antibody.

Whether ADAMTS13 deficiency is the sole cause of TTP is uncertain. Studies evaluating the role of ADAMTS13 deficiency in the presence of multimeric vWF imply that other factors may play a role in the pathogenesis of TTP.
Risk Factors

Apart from an inherited or acquired deficiency of ADAMTS13, other factors have been shown to be related to TTP exacerbations or acute episodes. These include pregnancy, HIV infection, and obesity. In addition, the use of several medications has been associated with TTP. These include antiplatelet agents (ticlopidine, clopidogrel), antineoplastic agents (mitomycin, cyclosporine and quinine), cocaine, as well as other drugs including antibiotics and statins.

Clinical/Laboratory Manifestations

Of the classic pentad, hemolytic anemia, thrombocytopenia, and neurologic symptoms are most frequently identified and are found in 74% of patients. Conversely, fever and renal involvement are identified in 40% of patients. The multitude of organ systems involved leads to varied symptomatology.

Hematologic

Thrombocytopenia

Platelet counts on average can be 25 x10^9/L, with approximately 55% of patients having a platelet count of less than 20 x10^9/L. Peripheral platelet destruction or utilization can be the cause of thrombocytopenia. Low platelets lead to the purpuric lesions, gingival bleeding, retinal hemorrhages, mucosal bleeding, and petechial hemorrhages.

Hemolytic anemia

Hemoglobin levels are usually greater than 10 g/dL, revealing a moderate anemia. Hemolytic anemia is suggested by a negative direct antiglobulin test (Coombs’s test). Other findings of hemolytic anemia include increased reticulocytes, LDH, indirect bilirubinemia, and decreased or absent haptoglobin levels. In addition, schistocytes on the peripheral blood smear are characteristic in patients with TTP. Presence of schistocytes in the peripheral blood of TTP patients varies from 0% to 18% of red blood cells.

Neurologic

Neurologic findings are the most common symptom and are identified in up to 75% of TTP cases. These can include confusion, headache, altered mental status, focal loss of motor or sensory functions, convulsions, stupor, and coma. Typically, neurological symptoms are transient and attributed to formation and dissolution of microthrombi in cerebral circulation. Because of their fleeting nature, the effects of TTP thrombi on cerebral circulation may be misdiagnosed as transient ischemic attacks.

Renal failure

Renal involvement is a predominant feature in HUS, but found in variable degrees in TTP. Proteinuria and hematuria are the cardinal features. Elevations of creatinine and serum BUN are milder on average when compared to HUS cases. However, acute severe TTP cases may present with a higher degree of renal involvement compared to mild or relapsing cases. For these patients, markedly elevated serum BUN on admission may indicate a poor prognosis.

Other Manifestations

Fever, though a part of the pentad, is not frequently found in TTP episodes. High fevers should alert the clinician of a possible infectious etiology.

Gastrointestinal. Microthrombotic lesions throughout the gastrointestinal tract can result in varying abdominal symptoms; abdominal pain is seen in 11 to 15% of patients. Pancreatitis is also seen as a result of TTP episodes.

Treatment

The mortality of TTP surpassed 90% prior to the use of plasma therapy. A recent study from Johns Hopkins University revealed as high as a 91% survival benefit when prompt initiation of treatment could be achieved. Additional findings in patients with severe TTP episodes showed that 83% of patients (20 of 24 patients with creatinine ranging from 1.4 to 10.8 mg/dl) had improvement of disease when treated with plasma exchange.

Mainstay of Therapy

Plasma exchange (PE) is the main treatment modality for TTP. Several studies propose its superiority to other modalities including plasma infusion (PI). The theory behind the use of plasma exchange lies in the removal of auto-antibodies against the ADAMTS13 as well as the large vW multimers, while simultaneously supplying missing or deficient plasma constituents, such as the metalloproteinase ADAMTS13. PE should be instituted within 24 hours of presentation, particularly in severely affected patients. If PE is not available, patients should be bridged by PI (at least 25 ml/kg per day). Optimal dosing of plasma exchange is still unknown. Single volume PE, in which patients receive a plasma volume that is the same as their predicted plasma volume, can be initiated at presentation. More intensive exchange regimens can be used in cases of resistant TTP by either increasing PE volumes to 1.5 times the predicted patient’s plasma volume or by performing twice daily PE of 1-1.5 plasma volumes. Daily PE should be continued until 2 days after remission; usually defined as normalization of neurological status, normal platelet count (> 150 x10^9/L), normal LDH values, and an increasing...
hemoglobin. Adverse events associated with plasma exchange include systemic infections, allergies or anaphylactoid reactions, pneumothoraces, hemorrhages, catheter associated thrombi, hypoxemia, hypotension, and serum sickness.

Ancillary Therapy

Glucocorticoid therapy has been shown to improve mild cases of TTP. Steroids are also used frequently during plasma exchange. Antiplatelet agents have shown no therapeutic advantage over plasma exchange. In addition, the use of antiplatelet agents may be associated with an increased bleeding risk; as a result, their use has largely fallen out of favor.

Though plasma exchange is still the preferred treatment modality for acute and relapsing cases of TTP, there exists a subgroup of patients with impaired response to this therapy. For such patients, other modalities may provide some benefit.

The use of vincristine in TTP predated that of plasma exchange. Recent studies indicate that its use may have therapeutic benefit in patients who do not respond to plasma exchange therapy, particularly if a persistent inhibitor is noted. Splenectomy is also used in the management of TTP. Some studies report no therapeutic benefit during the acute episode. However, others have claimed that when performed in remission, splenectomy leads to a decrease in the recurrence rate of TTP in patients with a history of relapse.

Summary

TTP is a rare condition, but one that carries a high mortality. Symptoms result from microthrombi affecting microcirculation and can be varied depending on the organs involved. The astute clinician must have a high index of suspicion for TTP in any patient presenting with hemolytic anemia and thrombocytopenia, particularly with concomitant fluctuating neurologic dysfunction. Not all characteristics of the classic pentad need to be present to raise suspicion or initiate therapy. The mainstay of therapy is plasma exchange, which may be used in conjunction with steroids. If plasma exchange is not readily available, plasma infusion can be initiated until plasma exchange is started. Other modalities that may provide therapeutic benefit in cases of relapsing TTP or in patients with slow or partial response to plasma exchange include vincristine and rituximab. Splenectomy done in remission may decrease recurrence in patients with relapsing TTP.

References

**Time for Reassessment: A Review of Beta-blockers in the Setting of Cocaine Associated Chest Pain and Acute Coronary Syndrome**

Jonathan Finkel MD and Gregory Marhefka, MD

**Introduction**

Cocaine is the second most commonly used illicit drug in the United States, and is the most frequent illicit substance to precipitate an emergency room visit, responsible for over 550,000 visits in 2007 alone. The majority of patients present with a chief complaint of chest pain, and approximately 6% are diagnosed with cocaine associated myocardial infarction. For decades it has been thought that beta-blockade in the setting of cocaine use would precipitate coronary vasospasm and worsen cardiovascular outcomes due to unopposed alpha receptor stimulation. In 1999 this thinking was incorporated into the ACC/AHA guidelines, which currently recommend beta-blockers in all patients with an acute coronary syndrome except in the setting of prior cocaine use. Recently there have been several studies suggesting benefit from beta-blocker administration in patients with cocaine associated chest pain and myocardial ischemia.

Given the recent data that call into question the validity of avoiding beta-blockers in patients with recent cocaine use, the goal of this article is to critically review the body of evidence that exists on beta-blocker usage in the setting of cocaine induced chest pain and myocardial ischemia.

Based on our findings it is clear that the current recommendations and theories need to be scrutinized and that additional outcomes based, randomized prospective human trials be conducted to effectively examine the possible benefits of beta-blocker usage in these patients.

**Methods**

We performed a comprehensive search of the medical literature concerning beta-blocker usage in the setting of cocaine intoxication, and cocaine associated chest pain and myocardial ischemia. The literature search was conducted using PUB Med and included English language publications from 1960-2010.

**Keywords:** Cocaine, beta-blockers, cocaine chest pain, MI, emergency department.

**Current ACC/AHA Guidelines For Beta-blockers in Acute Coronary Syndrome**

Beta-blockers have been shown by multiple large randomized trials to decrease mortality in patients presenting with cardiac ischemia and ST-elevation myocardial infarction (STEMI). In the ISIS-1 trial, more than 16,000 patients with suspected acute MI were enrolled within 12 hours of onset of symptoms. Subjects receiving atenolol therapy showed a reduction in 7-day mortality from 4.3% to 3.7% (p <0.02). In the Metoprolol In Acute Myocardial Infarction (MIAMI) trial, more than 5700 subjects with evolving MI were randomly assigned to receive placebo or metoprolol. Fifteen-day mortality was reduced with metoprolol from 4.9% to 4.3%. These trials form the basis of the ACC/AHA guidelines, which recommend beta-blocker therapy in all patients with STEMI, as well as NSTEMI/Unstable angina, as long as there are no contraindications.

**Beta-blocker Usage in the Setting of Cocaine Associated Chest Pain/ACS**

The guidelines go on to state that “Beta-blockers should not be administered to patients with STEMI precipitated by cocaine use because of the risk of exacerbating coronary spasm,” citing a review article by Klöner et al. published in Circulation in 1993. This article discusses the possibility of coronary vasoconstriction following beta-blocker administration in the setting of recent cocaine use, citing studies by Shannon et al. and Lange et al.

Shannon et al. administered cocaine followed by a beta-blocker to ten canine subjects while continually monitoring systemic and coronary hemodynamics. This study found that beta blockade in the setting of cocaine intoxication worsened coronary vasoconstriction, and decreased coronary blood flow.

Lange et al. conducted the only prospective human trial to examine the effect of beta-selective blockade on coronary artery hemodynamics in the setting of cocaine. This article is the primary source cited throughout the medical literature when discussing beta-blocker usage in the setting of cocaine chest pain and ACS. In this study, ten human subjects received intracoronary propranolol following intranasal cocaine administration. Similar to the canine study, Lange et al., found a significant increase in coronary vascular resistance, and a decrease in coronary sinus blood flow.

The only other human study that has looked at coronary blood flow following beta blockade in the setting of cocaine intoxication was published by Boehrer et al. three years after Lange’s article. This study looked at coronary artery area following intranasal cocaine and then administration of labetalol, a combination alpha and beta-blocker. Contrary to Lange’s findings, the nine patients that received cocaine followed by labetalol did not show a decrease in coronary artery area.

Thus, these three studies comprise the entirety of the literature evaluating this topic, and form the basis for the current national guidelines. With only two prospective human studies involving a total of 19 patients and contradictory results, it is not possible.
to draw a valid evidence-based conclusion on the cardiovascular effects of beta blockade in the setting of cocaine intoxication. More data regarding coronary perfusion as well as actual patient outcomes are needed before firm recommendations can be drawn regarding beta-blocker usage in this setting.

**Beta-blockers Effect on Systemic Hemodynamic Parameters and Outcome**

Though not specifically mentioned as a reason for beta-blocker avoidance in the ACC/AHA guidelines, beta-blockers in the setting of recent cocaine use have long been hypothesized to worsen systemic hypertension and tachycardia, and possibly precipitate myocardial ischemia due to increased cardiac oxygen demand. The mechanism is attributed to unopposed alpha-receptor stimulation leading to worsening systemic vasoconstriction. In this area, the evidence is equally inconsistent, with newer research concluding that beta-blockers may actually be beneficial in patients with cocaine associated chest pain and myocardial ischemia.

Sources that have shown worsening of hypertension, tachycardia, and cardiovascular outcomes secondary to beta blockade are scarce and have been confined to case reports, animal studies, and small retrospective case studies. In contrast, data demonstrating improved hemodynamics and cardiovascular outcomes from beta blockade following cocaine intoxication is derived from more recent research, with larger sample sizes, and in some cases prospective design.

One of the most compelling prospective studies favoring the use of beta-blockers in patients with recent cocaine use is a trial conducted by Hoskins et al., in which 90 patients with ACS and cocaine positive urine drug screen were randomized to labetalol or diltiazem. Both subject groups experienced similar and statistically significant decreases in blood pressure and heart rate, with no adverse outcomes occurring in any of the 60 patients that received combined alpha and beta-blocker therapy.

Rangel et al. conducted a retrospective cohort review looking at patients presenting with chest pain who were also found to have a cocaine positive urine drug screen. 331 patients were included, with 151 (46%) receiving beta-blocker therapy (85% received metoprolol). 19 Patients that received a beta-blocker in the emergency room (ER) had a significantly greater decrease in systolic blood pressure, and there was no difference in the rate of adverse outcomes, peak troponin levels, or EKG changes when compared with patients that did not receive beta-blocker therapy. There was also a post-hospitalization decreased mortality rate observed in the patients that received beta-blockers in the ER.

Recent data appear to show that selective beta-blockade as well as combination alpha and beta-blockade in the setting of cocaine intoxication do not increase the rate of negative outcomes. In fact most cases have shown improved hemodynamics and more favorable cardiovascular outcomes.

**Conclusion**

Given the strong evidence supporting the morbidity and mortality benefits of beta-blockers in patients undergoing ACS, and the weak and contradictory evidence opposing them in the setting of cocaine use it is necessary that steps are taken to better understand the issue. The majority of the recent data does not show any adverse cardiovascular outcomes, and the older data are equivocal at best.

We are possibly withholding beneficial treatment to patients based on unclear and outdated evidence. It is necessary to further examine the current treatment of cocaine related chest pain with prospective, randomized human trials to best determine what is optimal for patient outcomes.

**References**


**Paraneoplastic Pemphigus in a Patient with Carcinosarcoma of the Uterus**

Georgia Giebel, MSIV and Gunjan Shah, MD

**Case Presentation**

The patient is a 68-year-old female with hypertension, chronic obstructive pulmonary disease, without medical follow-up for several years, who initially presented with skin blisters and oral lesions, which were biopsied by her dermatologist and found to be bullous pemphigoid. She was treated with a course of oral prednisone and had resolution of her skin and oral lesions. Three months later, she presented with a swollen leg and was diagnosed with a deep venous thrombosis, for which she was started on coumadin and had an inferior vena cava filter placed. She then had hemoptysis a few days later, after which the coumadin was held. A chest computed tomography (CT) done at that time found a right middle lobe consolidation consistent with aspiration pneumonia and a cavitary lesion in the left upper lobe of her lung, which was biopsied and found to be a necrotizing cavitary lung lesion. After being ruled out for tuberculosis, she had an outpatient positron emission tomography (PET) scan which was positive for a 2.7 cm left lower lobe cavitary lesion and a 9 cm pelvic mass with hypermetabolic activity, as well as small liver lesions. Concurrently, she complained of dysphagia and 30-lbs of weight loss over the prior six months, so the decision was made to undergo an outpatient esophagogastroduodenoscopy (EGD). The EGD could not be completed secondary to a stricture in the distal esophagus; however, pemphigus ulcers were seen in the mouth and esophagus. Given the patient’s degree of malnourishment and dehydration, she was admitted to the outside hospital. On admission, she was found to have leukocytosis with a white blood cell count of 37,000/L, hypercalcemia with a calcium of 13mg/dL, hypotension, and acute renal failure with a creatinine of 4.4mg/dL. Her parathyroid hormone-related protein (PTHrP) was 105 pmol/L (normal <1.3 pmol/L), while her intact parathyroid hormone (PTH) was <3pg/mL (10-55 pg/mL). A serum protein electrophoresis with immunoelectrophoresis was positive for an IgG lambda paraprotein. On bone marrow biopsy, there were 25% plasma cells consistent with multiple myeloma, though this diagnosis was questioned after transfer. For treatment of her hypercalcemia, she was given intravenous fluids and calcitonin with minimal improvement, but with resolution of her renal failure.

The esophageal biopsy showed squamous mucosa with necrotic ulcer and chronic inflammation with fibrinous exudate. The pelvic mass was also biopsied which was consistent with carcinosarcoma with massive necrosis. The pathology revealed myxoid high-grade spindle cell sarcoma with pleomorphism and extensive mitosis and poorly differentiated adenocarcinoma with papillary serous differentiation, as well as some smooth muscle differentiation. During her hospitalization, the skin blisters reappeared and were biopsied. The biopsy was consistent with paraneoplastic pemphigus. She was treated with three days of intravenous immunoglobulin (IVIg). She had an open jejunostomy tube placed for nutrition. At this point, she was transferred to Thomas Jefferson University for further management.

Initial vital signs after transfer were within normal limits aside from mild tachycardia. On physical exam, she was lethargic, but oriented to person and place. She had a normal physical exam other than a II/V1 systolic ejection murmur, decreased breath sounds in her right lung base, and tenderness to palpation in the suprapubic region. She had no lymphadenopathy. A non-bleeding ulcer could be seen in her oral cavity, while her skin showed healing blisters (pictured below) without weeping. A pelvic exam was performed and a necrotic mass was found to be protruding into the cervix. Laboratory studies upon transfer included a white blood cell count of 32,800/L, hemoglobin 8.5 g/dL, platelet count 362/L, CA-125 1300 U/mL (normal 0-35 U/mL), creatinine 0.7 mg/dL, and calcium 9.9 mg/dL.

Dermatology was consulted and thought that her presentation was more consistent with paraneoplastic pemphigus given the combination of oral and skin lesions, rather than the previously diagnosed bullous pemphigoid. Hematology reviewed the initial bone marrow biopsy and concluded that it was more consistent with myeloma gammopathy of unknown significance. Gynecology/Oncology stated that her prognosis was poor and that her best option was palliative radiation, as she was not a surgical candidate secondary to metastatic disease. Her hospital course was complicated by an additional episode of hypercalcemia causing mental status changes, and she was effectively treated with a dose of pamidronate. After palliative radiation, the patient was transferred to hospice care.

**Figure 1. Healing skin blisters on abdomen**
A pauci-inflammatory subepidermal split can be seen at the lateral aspect of the punch biopsy. Our dermatopathologist believes that the split is not artifact, and represents abnormalities at the dermal-epidermal junction. This finding can also be seen in epidermolysis bullosa acquisita, bullous pemphigoid, other subepidermal bullous diseases, but taken in conjunction with the clinical history, it is consistent with paraneoplastic pemphigus.

**Discussion**

Paraneoplastic Pemphigus (PNP) is a rare, autoimmune blistering skin disorder, which occurs in the setting of a systemic neoplasm. The disease is characterized by polymorphous skin lesions, with a predilection for mucosal surfaces, along with evidence of IgG auto-antibodies against epidermal proteins. Paraneoplastic pemphigus was first described in 1990 by Anhalt et al.\(^1\), and since then there have been over 200 cases reported...
in the literature. Patients in all age groups have been affected by the disorder, including children and adolescents.2

Clinically, the presentation may be heterogeneous; however, mucosal lesions are inevitably present. Patients generally develop severe, painful stomatitis, and may have ulcerations and erosions of the oropharynx, larynx, esophagus, eyes, and genitalia.3 Cutaneous manifestations of the disease may vary in morphology. Skin lesions resembling erythema multiforme, graft-versus-host disease, lichen planus, as well as pemphigus and pemphigoid have been reported.1 Cutaneous findings generally appear after the onset of mucosal eruptions and may erupt in waves. Additionally, bronchiolitis obliterans may be a complication of PNP, often leading to respiratory failure and death.4,5 Bronchial inflammation and destruction with subsequent fibrosis appears to be caused by deposition of IgG autoantibodies on bronchial epithelial cell surfaces and basement membranes.6 Onset of dyspnea and dry cough in patients with paraneoplastic pemphigus should warrant prompt attention and therapy in order to avoid rapidly progressive respiratory complications.

PNP is associated with a variety of neoplasms. Lymphoproliferative disorders predominate, with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, Castelman’s tumor, and thymoma being the most common.7 Of note, PNP with monoclonal gammopathy has been reported as well.8 Non-hematologic neoplasms associated with PNP are liposarcoma, leiomyosarcoma, adenocarcinoma of the breast, colon, pancreas and other organs, basal cell carcinoma, and malignant melanoma.9 The histopathology in PNP varies according to the morphologic characteristics of the cutaneous lesions. Horn & Anhalt10 studied the histology of 16 biopsy specimens from six patients with PNP, and determined that there are a number of major features characteristic of the disorder. Acantholysis, or the loss of intercellular connections between epidermal cells, was commonly noted in the suprabasal region. Dyskeratotic keratinocytes, or the abnormal keratinization of skin cells characterized by eosinophilic, shrunken keratinocytes, was commonly seen at all epidermal levels. Suprabasal clefts or blisters reminiscent of those seen in pemphigus vulgaris, basal vascularization, and inflammatory cell exocytosis into the epidermis were other major features noted.10 The authors determined that both acantholysis and dyskeratotic keratinocytes at all levels of the epidermis indicate the presence of PNP.

A number of autoantibodies have been isolated in patients with PNP. Antibodies to the plakin family of proteins, which are structural proteins in hemidesmosomal and desmosomal plaques, have been reported.11 Anti-envoplakin and anti-periplakin have been noted to be the most specific autoantibodies.8 Anti-desmoglein-3 and anti-desmoglein-1 are also commonly isolated proteins. Autoantibodies may be detected using immunoprecipitation of antigen complexes, Western blot, and ELISA.11 It is likely that the diversity of autoantibodies accounts for the wide clinical spectrum of PNP.

Immunofluorescence, both direct and indirect, is an important component of the diagnosis of PNP. On direct immunofluorescence, deposits of IgG and complement in the epithelium are distributed both intercellularly and at the basement membrane zone.12,13 Indirect immunofluorescence may be used to detect antibodies in sera, utilizing monkey esophagus or rat bladder epithelium14. Using rat bladder as a substrate is more specific for PNP, as autoantibodies found in pemphigus vulgaris do not bind to transitional epithelia. However, indirect immunofluorescence may be negative in as many as one fourth of patients, and in this case, immunoprecipitation should be used to aid in the diagnosis.13

There have been a number of hypotheses regarding the pathogenesis of PNP. Xuejun and Bingxin14 isolated B-lymphocyte clones from a Castelman’s tumor, which specifically reacted to epidermal proteins, indicating that the associated tumors may produce auto-antibodies. Other authors have postulated that paraneoplastic skin eruptions promote exposure of self-antigens and subsequent development of auto-antibodies.15 Epitope spreading may then occur, where tissue damage exposes additional self-antigens, thereby diversifying the auto-antibodies to recognize additional proteins.16

Criteria for diagnosis were devised by Anhalt and colleagues in their original article.1 Those criteria have been revised into major and minor features. Major features include polymorphic mucocutaneous eruption, concomitant internal neoplasia, and characteristic serum immunoprecipitation findings. Minor criteria include evidence of acantholysis on histology, direct immunofluorescence staining of intercellular and basement membrane staining, and indirect immunofluorescence staining of rat bladder epithelium. Patients meeting all three major criteria and at least two minor criteria should be considered to have PNP.17

Treatment of PNP includes early detection and resection of the associated tumor, especially in the case of Castelman’s disease. Intravenous immunoglobulin (IVIg) should be administered before, during, and after the operation.14 Immunosuppression is an important component of treatment of PNP, and high-dose corticosteroids are first line.17 Cyclosporine, azathioprine11, mycophenolate mofetil,18 and other steroid-sparing agents may be used as adjunct therapy. If these agents fail to control the disease, alternative agents such as plasmapheresis, IVIg19, and rituximab19,20 have been used with mixed results. Unfortunately, response to treatment is generally poor, and PNP frequently results in premature death compared to the average life expectancy associated with the underlying malignancy.3,15 The prognosis is generally more favorable in patients with benign neoplasms, such as Castelman’s syndrome or thymoma.3

In summary, paraneoplastic pemphigus is a rare, polymorphous blistering disease with a predilection for the mucosal surfaces in the setting of an associated neoplasm. The disease should be suspected if histology demonstrates acantholysis and
dyskeratotic keratinocytes, and if characteristic immunofluorescence is noted. Prompt diagnosis and treatment, along with search for underlying neoplasm, is appropriate as progression of the disease can result in death.

References

"Parc de la Ciutadella, Cascada Fountain", photograph by Paurush Shah, MD
A Case of Metastatic Breast Cancer to the Meninges
Carolyn M. Ross, MSIII and Jie Cui, MD

Case Report

A 44-year-old woman with a history of triple-negative breast cancer metastatic to the brain presented with changes in mental status, lower back pain, and a left facial Bell’s palsy.

The patient had previously been ambulatory and fully cognizant of her surroundings until one week prior to presentation when she began to exhibit progressively worsening confusion. As her mental status began to change, the patient developed new onset pain over her lumbar spine, supra-pubic area, bilateral flanks, hips, and knees. The pain was refractory to an epidural injection into her lumbar spine performed at the patient’s local hospital. Other complaints included a recent onset urinary retention, weakness of the left lower extremity, a left facial Bell’s palsy, and difficulty walking. On admission, the patient was taking gabapentin, citalopram, aspirin, enoxaparin, lopressor, docusate, lorazepam, and methylprednisone. The patient was treating her pain with hydromorphone hydrochloride as needed. No other medications had recently been prescribed.

Past medical history included breast cancer status post bilateral mastectomies, four cycles of chemotherapy with paclitaxel, and neo-adjuvant radiation. One month prior to presentation, the patient was found to have metastases to her brain, and underwent a left fronto-temporal craniotomy that was then followed by a course of whole brain irradiation.

Upon examination, the patient was confused and had difficulty speaking and swallowing. Her temperature was 97.4°F, her pulse was 95 beats per minute, her respiratory rate was 20 breaths per minute, and her blood pressure was 143/88 mm Hg. The patient’s pulse oximetry on room air was 95%. Her pupils were anicteric and equally round and reactive to light, but a left visual field defect was noted. The patient exhibited facial nerve palsy involving the entire left side of the face. All other cranial nerves appeared intact. The patient showed diffuse myoclonic jerks in her upper extremities. Motor testing revealed 3/5 strength in the left lower extremity, a left facial Bell’s palsy, and anacloric weakness of the left lower extremity, a left facial Bell’s palsy, and difficulty walking. On admission, the patient was taking gabapentin, citalopram, aspirin, enoxaparin, nystatin, lopressor, docusate, lorazepam, and methylprednisone. The patient was treating her pain with hydromorphone hydrochloride as needed. No other medications had recently been prescribed.

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The patient’s white blood cell count was 6300 cells/mm³ with a differential of 76.3% neutrophils and 11.9% lymphocytes. Hemoglobin was 13.5 g/dL, hematocrit was 40.4%, and platelets were 229,000/ml. Electrolyte values and coagulation tests were both within normal limits. The patient’s ESR was elevated at 60. Her liver function tests showed a total protein of 6.9 g/dL, albumin of 4.2 g/dL, total bilirubin 1.4 mg/dL, direct bilirubin 0.6 mg/dL, AST of 33 U/L, ALT 32 U/L, and alkaline phosphatase of 82 U/L. Blood and urine cultures were negative for bacterial growth.

A CT scan of the patient’s spine revealed mild multilevel degenerative changes with no evidence of lytic or blastic lesions. An MRI of the spine showed no evidence of bony metastases, spinal cord compression, or significant spinal stenosis, and a long bone scan was also negative for any bone lesions. A head CT scan was negative for intracranial hemorrhage, mass effects, vasogenic edema or midline drift. A brain MRI was notable for thick nonspecific dural enhancement along the left anterior frontal convexity.

After admission, the patient’s mental status continued to rapidly decline. A lumbar puncture was performed and cerebrospinal fluid analysis revealed low glucose of 13 mg/dL, increased protein of 256 mg/dL, chloride of 115 mg/dL, and a pH of 7.97. Red cell count was 155 cells/µL, and white cell count was 14 cells/µL, with a differential of 14% neutrophils and 68% lymphocytes. A cryptococcal antigen test of the CSF fluid was nonreactive and cytology results of the CSF fluid were non-diagnostic. The clinical picture was suggestive of a diagnosis of leptomeningeal carcinomatosis.

Neuro-oncology was consulted regarding the patient’s potential for intrathecal chemotherapy treatment. Unfortunately, her condition was deteriorating so rapidly that the family opted for palliative care management, and the patient expired soon afterwards in the hospital.

Discussion

Carcinomatosis is a condition in which cancer spreads diffusely throughout the body, and can take place in both the peritoneum and the leptomeninges. Leptomeningeal carcinomatosis (LC), also known as neoplastic meningitis, occurs when a patient’s cancer metastasizes to the meninges surrounding the spinal cord and spreads diffusely throughout the subarachnoid space to produce multifocal neurological signs and symptoms. It is an end-stage cancer phenomenon, and a relatively rare metastasis.

Malignant cells can metastasize to the meninges in several ways. Hematogenous spread is the most common route, but this type of entry is more often seen in hematologic malignancies like leukemia than in solid primary cancers. Solid tumors tend to spread through lymphatics to reach the meninges, and enter the subarachnoid space by passing through the dural and arachnoid coverings of spinal and cranial nerve roots. Other pathways described include direct spread from metastases in the CNS parenchyma, as well as iatrogenic spread through an accidental ependymal or dural breach created by a neurosurgical procedure. No matter the route, once malignant cells gain access to the CSF, they seed the meningeal surface by CSF flow and grow to form deposits that can appear either diffusely thin, or plaque-like and...
Case Reports

The cancerous cells can then invade the pial membrane to reach the spinal nerves, cranial nerves, and spinal cord, resulting in the multifocal neurologic symptoms that characterize the metastasis.

LC is diagnosed clinically in 5-8% of solid tumor cancer patients and in 5-15% of patients with leukemia/lymphoma. However, autopsy results of cancer patients who showed neurological signs and symptoms prior to death have revealed undiagnosed LC in 20% of cases. This can be explained by the fact that LC is usually an end-stage complication of metastatic cancer; confusion and pain are common in terminal cancer patients, so many cases of symptomatic LC may be overlooked in the late stages of metastatic cancer.

The most common causes of LC are breast and lung cancer, even though other rare malignancies may be more inclined to metastasize to the meninges; this is because breast cancer patients have a longer life expectancy and a larger patient population. Incidences of LC in different cancer populations are as follows: melanoma >23%, small cell lung cancer 6-25%, leukemias 10%, lymphomas 7%, breast cancer 2-5%, and non-small cell lung cancers 1-5%.

It has been noted recently that the incidence of LC has been increasing in both the breast and lung cancer populations. This phenomenon can be explained by several causes. Ongoing improvements in cancer treatment have led to better systemic control of cancer and longer patient survival time, which allows for LC to occur in the end stages of the disease. In addition, many popular chemotherapeutic drugs will not cross the blood-CSF barrier; thus, while the patient is being treated systemically, any therapeutic agents are taxanes and trastuzumab, both of which are commonly utilized in breast and lung cancer. Finally, there is an increased rate of clinical diagnosis of LC due to heightened physician awareness and neuro-imaging studies that can help to confirm the suspicion.

Multifocal neurological symptoms are the classic presentation of LC, but clinical signs can be absent in at least 25% of patients at time of diagnosis. Patients most commonly complain of headache, change in mental status, confusion, facial and auditory deficits, diplopia, back pain, and lower extremity numbness or weakness. 15% of patients will show signs and symptoms associated with cerebral hemispheric dysfunction (headache, dizziness, nausea/vomiting), 35% of patients will show signs and symptoms associated with cranial nerves (diplopia, facial nerve palsies), and 60% of patients will show signs and symptoms associated with the spinal cord and nerve roots (radicular pain or weakness, urinary incontinence or retention).

Early diagnosis of LC is essential to prevent further complications and neurological damage, and so all patients suspected of having the disease should receive a lumbar puncture and an MRI of the spinal cord. Classic CSF findings in LC include elevated protein concentration, lymphocytic pleocytosis, and decreased glucose concentration, which were all seen in our patient. MRI findings suggestive of LC include cranial nerve, subependymal, and leptomeningeal enhancement. While CSF cytology with evidence of malignant cells remains the gold standard for diagnosis, cytology results are positive upon first lumbar puncture in only 54% of LC patients, and may remain falsely negative in up to 14% of LC patients after even three CSF samplings. Cytology is more likely to prove the existence of LC when meningeal involvement is diffuse or when the sampling site is closer to the site of the main focus of metastasis. Even if cytology of the CSF is non-diagnostic, and there exists an opening pressure above 15 cm H2O, an elevated white blood cell count, a protein concentration greater than 50 mg/dL, or a glucose concentration less than 60 mg/dL, LC remains a likely cause of the patient’s symptoms. Therefore, in advanced cancer patients with multifocal neurological symptoms, typical MRI image findings, and suggestive CSF fluid analysis, the diagnosis of leptomeningeal carcinomatosis is quite straightforward.

Treatment of leptomeningeal carcinomatosis requires a multidisciplinary approach. The current goal of therapy is improvement or stabilization of patients’ neurologic symptoms. Therapeutic approaches include intrathecal chemotherapy (mainly with methotrexate), radiotherapy of the meninges, systemic chemotherapy with drugs that penetrate the CSF, and surgery to relieve increased intracranial pressure. A recent study has shown that systemic chemotherapy, intrathecal chemotherapy, and whole brain radiation all have a positive impact on patient survival, while radiotherapy of the spinal meninges does not influence patient survival time. While radiotherapy and intrathecal chemotherapy were once the mainstays of LC treatment, systemic chemotherapy (utilizing drugs that can penetrate the subarachnoid space) is gaining popularity as a therapeutic option, as it treats both the meningeal carcinoma as well as the systemic malignancy. Recent recommendations for the treatment of LC suggest focal radiation first to debulk any tumors, followed by a course of chemotherapy. Solid tumors have a propensity to attach to neural structures in the form of bulky nodules, while hematologic malignancies tend to spread more diffusely along the meninges. The leptomeningeal nodules caused by the spread of solid tumors are more likely to show up as areas of enhancement on MRI. Intravenous systemic chemotherapy is preferred in patients who have multiple nodules or MRI evidence of leptomeningeal enhancement, and intrathecal chemotherapy is preferred in patients with positive CSF cytology but negative MRI scans.

Aggressive treatment is unlikely to improve neurologic symptoms in many patients; indeed, neurologic toxicity can result, instead. In these patients, palliation may be the best option. If left untreated, the median survival time of LC patients is 3-6 weeks. With treatment, median survival time is variable, ranging from 7-16.5 weeks depending on the patient’s performance status and primary tumor site. Of the LC patients who die, 24-34% die from progression of the leptomeningeal...
carcinomatosis itself, 22-25% die from progression of both LC and the systemic disease, and 19-44% die from progression of the systemic cancer alone. Several prognostic factors have been indicated in response to treatment, including age, tumor type, and neurological status at time of diagnosis. A series of studies of LC patients demonstrated that 61% of breast cancer patients showed a neurological stabilization or advancement with radiation and chemotherapy, while only 39% of lung carcinoma and 18% of melanoma patients achieved similar results. Patients with breast cancer as their primary malignancy have been shown to have the best prognosis of all patients with leptomeningeal metastases, and are consequently most likely to benefit from aggressive treatment.

References


“Citadel of Cairo, Egypt”, photograph by Sameh Gaballa, MD
West Nile Virus Encephalitis in a Patient with Renal Transplant

Charles-Lwanga Bennin, MD, Steve Krawitz, MD and Emma Weaver, MD

Introduction

Most cases of West Nile Virus infection are asymptomatic. 60% to 70% of neuro-invasive cases of West Nile virus infection result in meningitis or encephalitis; however, West Nile encephalitis occurs in less than 1% of patients infected with the West Nile virus.1

Case

Our patient is a 60 year old Caucasian female with a history of antiphospholipid syndrome, an ischemic stroke in 1994 resulting in warfarin therapy, hypertension, end stage renal disease secondary to idiopathic glomerulonephritis status post cadaveric renal transplant in 1995 on immunosuppressive therapy. She presented with multiple febrile episodes and subjective chills one day prior to admission. She was alert and oriented to person, place and time, but appeared weak. She had no nuchal rigidity and cardiovascular and pulmonary examinations were within normal limits.

On admission she was on the following medications: mycophenolate 1gm every 12 hours, daily administration of atenolol 25mg, warfarin 4 mg daily, duloxetine 30mg, and lorazepam 0.5 mg as needed for anxiety. She had no known drug allergies. Her family history was unremarkable and she denied the use of alcohol, tobacco, or illegal substances. Laboratory values on admission are presented in Table 1.

She was admitted for fever workup. On hospital day 2, she had a change in mental status, and therapy was initiated for presumptive bacterial and viral meningitis, encephalitis, and bacterial sinusitis. Computed tomography (CT) scan of the head showed encephalomalacia and gliosis in the right posterior frontal lobe and right basal ganglia. There was no new hemorrhage, mass effect, midline shift or edema. With worsening mental status, she was transferred to the intensive care unit (ICU) for closer monitoring. She never required ventilator support. She was later transferred to the general floor after 3 days in the ICU when her mental status improved. She subsequently had an abrupt worsening in her mental status. She also continued to have febrile episodes (Figure 1). A magnetic resonance imaging (MRI) of the brain also revealed cerebral volume loss.

She was re-admitted to the ICU and later transferred to the Neurology ICU (NICU). A lumbar puncture (LP) was performed on hospital day 2, 13 and 17. Each sample of cerebrospinal fluid (CSF) was sent for polymerase chain reaction (PCR) (analysis of Mycobacterium tuberculosis, Herpes simplex virus (HSV), Cytomegalovirus and JC virus; Lyme (IgG, IgM), Toxoplasma IgG; fungal, bacterial culture and India ink for Cryptococcus which was all negative.

The ELIZA assay for CSF West Nile virus from hospital day 13 returned positive; however repeat testing on hospital day 13 revealed elevated IgG of 2.03 (normal <1.3) and elevated IgM of 5.27 (normal <0.9). All antibiotics were stopped on hospital day 22. She later regained her mental status and was almost back to her mental baseline. She was transferred out of the NICU on hospital day 25.

Discussion

In the West Nile region of northern Uganda the first isolate of an arbovirus was obtained from a febrile woman. The first reported case of West Nile encephalitis was in the early 1950s in New York resulting from an experimental treatment for advanced cancer.1 Almost forty years later, in 1999, cases of West Nile encephalitis appeared in clusters in the United States2 with multiple cases having been documented thereafter. Typically these cases peak in the warm months of the year in the northeast in the months of July to October.3 The West Nile virus is a single stranded RNA flavivirus. The carriers of this virus are usually migratory birds that have been bitten by an infected Culex mosquito (Figure 2).

In most patients infected with the West Nile virus, there is on average a 10±5 days incubation period. In a subset of infected individuals such as immunocompromised patients, viral incubation can last up to 21 days.4 The most common clinical presentation includes fever with a viral prodrome, however tremors although uncommon can also be seen.5 The sensitivity of ELISA to detect West Nile IgM increases based on the timing of the sample, as successful isolation decreases as the disease duration progresses.5 In West Nile encephalitis the virus crosses the blood brain barrier and hence detection involves analysis of the CSF. Real time PCR detects the infection in about half of infected patients.6 IgM detection is the most common and preferred test of choice. In addition to CSF and serum analysis

Table 1. Laboratory Values on Admission

<table>
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<tr>
<th>Laboratory Value</th>
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<th>Normal Range</th>
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<td>Potassium</td>
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<td>HCT</td>
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of IgM, imaging modalities such as MRI or CT of the brain may be helpful in identifying the presence of central nervous system inflammation.

**Conclusion**

Other causes of encephalitis or meningitis such as HSV and Lyme disease should be ruled out prior to initiating treatment for West Nile encephalitis. As shown in Figure 1, antiviral or antibiotics have no effect on febrile episodes and treatment is generally supportive. Complications such as cerebral edema, headaches can occur after infection. Our patient had residual persistent limb weakness which was managed with physical therapy.

**References**

Acute HIV, Rhabdomyolysis, Renal failure, and Hepatitis: A Case Report

Eve R. Merrill, MD

Case Report

A 19 year old African-American male with no significant past medical history presented to an outside hospital with two days of diffuse abdominal pain, myalgias, muscle weakness, and dark urine. Two weeks prior to presentation, the patient was treated as an outpatient with an unknown antibiotic for symptoms of a sore throat, nausea, and non-bloody, non-bilious emesis. The patient denied any sick contacts, recent travel, trauma, strenuous exercise, or the use of non-steroidal anti-inflammatory drugs, acetaminophen, alcohol, or illicit drugs. The patient reported being sexually active with one female partner and had no history of sexually transmitted infections. The patient was employed at a daycare center.

Vital signs and physical exam findings from the outside hospital were unavailable. Laboratory studies from the outside hospital showed a creatine phosphokinase (CPK) of 64,000 IU/L and a serum myoglobin of 37,036 ng/ml, consistent with rhabdomyolysis. Urinalysis demonstrated 3+ blood and 13 red blood cells. The patient was also in acute renal failure with a blood urea nitrogen of 44 mg/dL and creatinine of 6 mg/dL. The patient was oliguric and uremic so hemodialysis was initiated at the outside hospital. The patient’s labs were also significant for a transaminitis with an aspartate aminotransferase of 5,642 IU/L and an alanine aminotransferase of 543 U/L. All other liver function tests were within normal limits. The patient had a negative urine drug screen and group A streptococcus rapid test. Viral testing for influenza A & B, respiratory syncytial virus, Epstein-Barr virus (monospot), and HIV (ELISA) were all non-reactive. The patient was transferred to Thomas Jefferson University Hospital for a liver transplant evaluation and further management.

Hospital Course

Upon arrival to TJUH, the patient was afebrile (98.4°F), pulse of 99 beats per minute, blood pressure of 154/90 mmHg, a respiratory rate of 24 breaths/min, and a pulse oximetry of 99% on room air. On review of systems, the patient complained of abdominal pain, myalgias, and fatigue. On physical exam, the patient appeared tired and ill. His abdomen was soft and mildly tender to palpation in all four quadrants. The patient had diffuse muscle tenderness but no joint effusions. His bilateral upper and lower extremities had non-pitting edema that extended to the elbows and knees. Upper extremity strength was 4/5 bilaterally while lower extremity strength was 3/5. The patient had no rashes, ulcers, asterixis, or jaundice. The rest of his physical exam was unremarkable. The labs on admission to TJUH showed a creatine phosphokinase of 234,417 IU/L, aspartate aminotransferase of 2,218 IU/L and alanine aminotransferase of 453 IU/L. The blood urea nitrogen was 53 mg/dL and the creatinine was 8 mg/dL. The patient had a hemoglobin of 11.8 g/dL, a white blood cell count of 3.7 B/L and platelets of 160 B/L. Urine studies demonstrated myoglobin, 3+ protein, 3+ blood, 158 red blood cells, no casts, and 3 white blood cells.

The patient continued to get daily dialysis while the primary team investigated the etiology of the patient’s rhabdomyolysis, acute hepatitis, and acute renal failure. The patient’s rhabdomyolysis and transaminitis improved throughout the hospitalization. Abdominal ultrasound of the liver showed no hepatomegaly but demonstrated prominent periportal walls, suggestive of inflammation. Since the patient’s hepatic function was improving, the liver transplant team did not consider the patient a candidate for a liver transplant.

The patient’s renal function was evaluated and renal ultrasound revealed mildly enlarged echogenic kidneys and no hydronephrosis. Renal biopsy was consistent with acute tubular necrosis and showed normal glomeruli, diffuse dilatation of the proximal tubules, myoglobin containing casts, and granular eosinophilic casts. Although the patient was initially oliguric, his urine output improved during the hospitalization. He continued to require hemodialysis at discharge though the nephrologists were hopeful that this would only be temporary.

Autoimmune, rheumatologic, and infectious etiologies were further explored. Autoimmune labs for antinuclear antibody, antimitochondrial antibody, c-antineutrophil cytoplasmic antibody, p-antineutrophil cytoplasmic antibody, and anti-liver-kidney microsome antibodies were all negative. Complement values were both within normal limits with a C3 of 81 mg/dl and a C4 of 15 mg/dl. Hepatitis A, B, and C serologies, herpes simplex virus antibodies, rotavirus Ag, and enterovirus stool RNA were all negative. The patient’s throat, urine, blood, and stool cultures all showed no growth.

An HIV (ELISA) test was repeated to check for seroconversion. The HIV test was positive, the HIV RNA viral load was 273,000 copies/mL and the CD4 count was 290 cells/mm³. The patient was diagnosed with an acute HIV infection that caused a viral myositis. The viral myositis stimulated rhabdomyolysis, which in turn produced acute tubular necrosis and transaminitis.

Discussion

Rhabdomyolysis is the breakdown of skeletal muscle and the release of the myocyte’s intracellular components, including creatine phosphokinase and myoglobin. Of note, myoglobinuria is not required for the diagnosis of rhabdomyolysis. Causes of rhabdomyolysis include trauma such as crush injuries, non-infectious sources (drugs, rheumatologic disorders, toxins) as well as infectious etiologies. Infectious sources include influenza, streptococcus, coxsackie virus and HIV.
Patients infected with HIV have three stages in which rhabdomyolysis occurs. Most frequently, rhabdomyolysis is seen as a late manifestation of advanced AIDS when the HIV RNA stimulates lymphoid cells and inflammation around the myocytes. Second, rhabdomyolysis may also develop as a side effect of an antiretroviral medication during a chronic HIV infection. Typically, a primary HIV infection presents with mononucleosis or flu-like symptoms that include myalgias. In rare cases, rhabdomyolysis may result from acute HIV seroconversion. The exact mechanism in which acute HIV causes a viral myositis is not clear. Some possible explanations include the virus’ direct invasion of the myocytes or viral-induced inflammation with the release of pro-inflammatory mediators.

In order to make a definitive conclusion that an acute HIV infection induced rhabdomyolysis, a clinician must rule out other potential causes of rhabdomyolysis. For our patient, we ruled out many common viral and bacterial infectious causes as well as legal and illegal drugs, toxins, and rheumatologic disorders. Cytomegalovirus is a well-established cause of acute rhabdomyolysis. Medical literature contains very few case reports that can attribute acute HIV as the sole cause of rhabdomyolysis as the patient either had a co-infection with CMV or the patient was not tested for CMV. A literature review by McDonagh and Holman identify 23 case reports that attribute acute HIV as the etiology of rhabdomyolysis. However, when excluding cases in which the patient is co-infected with CMV or has another plausible explanation for rhabdomyolysis, McDonagh and Holman can only attribute four cases of rhabdomyolysis to acute HIV. Our patient tested positive for the CMV IgG Ab (9.72 IV) indicating a current or past CMV infection. Thus, we cannot exclude the possibility that CMV, and not HIV, was the infectious agent that produced the patient’s rhabdomyolysis. Although it may be rare, a patient who presents with acute rhabdomyolysis should be evaluated for a primary HIV infection, especially when another etiology cannot be identified. As in the case with our patient, an HIV test should be repeated as rhabdomyolysis may occur during the acute seroconversion period when the ELISA test may still be negative.

References
A 52-YEAR-OLD FEMALE WITH RAMSAY HUNT SYNDROME

Ketki Soin, MSIII, Eric Struble, MD and Whitney Jackson, MD

Case Report

A 52 year-old female with a history of poorly controlled type II diabetes and a recent admission of right-sided pre-septal orbital cellulitis presented with a facial rash and severe ear and eye pain for three days. The patient noted sudden right-sided vision loss and associated right-sided face, ear and eye pain three days prior to admission. The pain was a 9/10 and was worsening since its onset. Upon questioning she also noted decreased taste sensation. She denied tinnitus, vertigo, hearing loss, nausea, vomiting, or fevers.

On physical exam, the patient was afebrile, she had a heart rate of 102 beats per minute, a blood pressure of 122/57 mmHg, and an oxygen saturation of 94% on room air. Her skin exam was remarkable for a macular rash on the right side of her face in a dermatomal distribution, extending from her mouth to the external ear and continuing to her neck. She had vesicular lesions on her nose, known as Hutchinson’s sign. Her ear exam showed erythema of the right ear, swelling of the pinna and auricle, and multiple vesicles present on her right tympanic membrane and external auditory canal. Her eye exam was significant for no light perception in the right eye with erythema and edema of her right eyelid. Neurological exam was remarkable for cranial nerve II, VI, and peripheral VII palsies. Weber test lateralized to the left ear and the Rhine test was positive bilaterally. On admission, laboratory studies revealed a white blood cell count (WBC) of 10.0 B/L. The differential included 73.4% neutrophils, 13.4% lymphocytes, and 7.6% monocytes. Other significant studies were a hemoglobin A1c of 13.7%, glucose of 388 mg/dl and a creatinine level of 1.6 mg/dl.

The patient was admitted and treated with IV acyclovir, IV methylprednisolone, fluids and insulin drip at 4 units/hr was initiated. During her hospital stay, an MRI of the brain and orbits was performed to rule out meningeal involvement. The MRI showed abnormal enhancement of the right optic nerve sheath without meningeal involvement (Figure).

The patient’s hospital course was complicated by difficult-to-control diabetes. Her glucose levels ultimately normalized with very high insulin requirements. Over the course of her hospitalization, insulin and methylprednisolone were tapered. She was discharged one week after admission once her ear and eye pain resolved and her glucose levels normalized. Despite therapy with acyclovir and corticosteroids, the patient’s peripheral facial palsy and vision changes did not resolve in the hospital. She was to follow-up with the neuro-ophthalmology office as an outpatient.

Discussion

The varicella zoster virus is known for two classic clinical syndromes: varicella or chicken pox is the primary infection, while zoster or shingles is the reactivation of latent infection
in the dorsal root ganglia. However, other complications of herpes zoster exist; these include cranial nerve palsies, herpes zoster ophthalmicus, acute retinal necrosis, aseptic meningitis, encephalitis, or stroke syndromes secondary to cerebral artery infection. Ramsay-Hunt syndrome, herpes zoster oticus, is facial and auditory involvement due to reactivation of herpes zoster in the geniculate ganglion. This rare manifestation of herpes zoster causes painful vesicles in the external auditory canal, loss of taste in the anterior one-third of the tongue, ipsilateral facial palsy, and it may be associated with herpes zoster ophthalmicus, threatening visual loss.

The incidence of Ramsay Hunt syndrome is less than 1% of all patients with herpes zoster. In a review of 859 patients with herpes zoster, complications including Ramsay-Hunt, postherpetic neuralgia, superinfection, ocular involvement, Bell’s palsy and meningitis were associated with advanced age and comorbidities including diabetes, HIV, cancer and transplant recipients. HIV and transplant recipients present with more complications.

Antiviral agents and corticosteroids are first line therapies for herpes zoster with cranial nerve involvement. Antiviral therapy may improve outcomes by prohibiting progression of the varicella virus and reducing long-term nerve damage. It has even been suggested that antiviral therapy can improve outcomes of facial weakness in Ramsay Hunt syndrome, however there is little data to support this. In a retrospective review of 26 patients with herpes zoster oticus, all were treated with Acyclovir, with 84% showing recovery. There was no control group; age and diabetes mellitus were identified as poor prognostic factors.

Steroids, presumably, are also beneficial in treatment in that they have anti-inflammatory effects, which limit neural edema and subsequently, tissue damage and cell death. It is therefore logical that both steroids and antiviral treatment together should be used to treat zoster. In a study by Kinishi and colleagues, 91 patients were treated with acyclovir and corticosteroids compared to 47 patients treated with corticosteroids alone. Voluntary facial movement recovered in 82 of the 91 patients (90%) treated with both acyclovir and corticosteroids compared to 30 of the 47 patients (64%) treated with corticosteroids alone.

Timing of treatment also seems to play a critical role in recovery Ramsey Hunt patients. In an observational study of 81 patients, administration of both steroids and acyclovir within 3 days of onset of symptoms showed full recovery of deficits in 21 out of 28 patients (75%). When treatment was initiated between days 4 and 7 of symptom onset, 14 of 29 patients (48.3%) showed absolute resolution. For those that received treatment after 7 days, full recovery was achieved in only 7 of 23 patients (30.4%).

However, this data has not been convincingly replicated. Recent Cochrane reviews question the role of acyclovir, other antivirals, and corticosteroids in herpes zoster oticus treatment and outcomes. Only one randomized controlled trial was included in the Cochrane Review looking at antiviral therapy vs antiviral therapy with corticosteroids for treatment of Ramsay-Hunt syndrome. It included only 15 patients and there was no statistically significant difference between the two groups. No randomized, controlled trials exist looking at corticosteroid treatment for Ramsay Hunt. After thorough literature review, they conclude that there is currently insufficient randomized, controlled trial data to provide evidence for or against standard antiviral therapy alone or in combination with steroids for the treatment of Ramsay Hunt syndrome.

References

**Brain Zygomycosis in a Patient with High Risk Myelodysplastic Syndrome after Initiation of Chemotherapy**

Sameh Gaballa, MD1 and Ali Al-Ameri, MD2

1 Thomas Jefferson University Hospital, Department of Internal Medicine; 2 University of Texas MD Anderson Cancer Center

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**Introduction**

Zygomycetes are a group of fungi that can cause a variety of life-threatening infections particularly in immunocompromised patients. Zygomycosis manifests as a spectrum of diseases including stroke.1-3 We present a case of disseminated zygomycosis with central nervous system (CNS) involvement in a patient with myelodysplastic syndrome (MDS) after initiation of chemotherapy.

**Case report**

A 46-year-old female with a history of diffuse large B-cell lymphoma status post autologous stem cell transplantation developed high risk MDS, which was thought to be secondary to her treatment. She had received induction chemotherapy with idarubicin, cytarabine and vorinostat (suberoylanilide hydroxamic acid) and was discharged. She was then readmitted to the hospital after developing fevers and diarrhea. After admission, she continued to be febrile despite broad-spectrum antibiotics and antifungal drugs. She had been on fluconazole prophylactically and it was subsequently switched to posaconazole upon admission. While on the floor, she developed hemiplegia, hemineglect, dysarthria, mental status changes, and respiratory distress and was transferred to the intensive care unit. The chest x-ray showed bilateral pulmonary infiltrates and CT of the brain revealed multiple hypoattenuated lesions with associated marked edema scattered throughout the brain. Follow-up CT of the brain showed a mild midline shift. MRI of the brain reported multiple supratentorial and infratentorial masses producing ring-enhancing lesions that are centrally

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Figure 1: MRI of the brain showing multiple masses producing ring-enhancing lesions with central hemorrhagic changes (A, B). CT of the brain showing multiple slightly heterogeneous, hypodense lesions scattered throughout the brain parenchyma (C, D).
hemorrhagic, suspicious for high-grade tumor or an ischemic process (Figure 1). The patient was started on liposomal amphotericin B in addition to voriconazole. A lumbar puncture was not performed for fear of causing uncal herniation. Her condition continued to deteriorate and she died in the ICU. Autopsy revealed multiple hemorrhagic areas in the cerebrum and diencephalon along with a 1 cm hemispheric lesion in the cerebellum. Microscopic examination identified fungal hyphae involving cerebral vessels with extension into the parenchyma of the cerebrum and cerebellum. The lungs, liver, spleen and kidneys showed disseminated intravascular fungal infection consistent with zygomycosis.

Discussion

Infection with zygomycetes is usually acquired through inhalation of spores and can cause aggressive rhino-orbital-cerebral and pulmonary disease in diabetic or immunocompromised individuals. Risk factors include diabetes mellitus, hematologic malignancies, neutropenia, drug-induced immunosuppression, solid organ or bone marrow/stem cell transplantation, and intravenous drug use. The patient had iron overload secondary to repeated blood transfusions for underlying MDS and some reports have suggested that iron overload might be a risk factor for Zygomycetes.1-8

There have been several reports of disseminated zygomycosis in patients with leukemia, lymphoma, intravenous drug abuse and HIV.9-11 The disease should be suspected in high-risk individuals who present with sinusitis, altered mentation and/or necrotic tissue in the nose or palate. A high index of suspicion is essential for early diagnosis and treatment. Endoscopic evaluation of the sinuses should be performed to look for tissue necrosis and obtain specimens. Cultures often yield no growth and histopathological identification of zygomycete may provide the only evidence of infection.

The CNS is typically involved as a direct spread from infected paranasal sinuses, or rarely through hematogenous spread in disseminated disease in immunocompromised patients. Zygomycosis of the CNS can present in three distinct clinical forms: rhinocerebral zygomycosis, disseminated zygomycosis with CNS involvement, and isolated cerebral zygomycosis. Zygomycosis fungus has a high affinity for blood vessels, particularly for the elastic membranes.

Fatal ischemic strokes caused by major artery occlusion by zygomycosis have been reported previously.1,2 A few cases have reported intracranial hemorrhage in patients with zygomycosis.3,12,13 We present a case of disseminated zygomycosis with CNS involvement presenting clinically as stroke and radiographically as a hemorrhagic mass. Although the patient received posaconazole and amphotericin B, she succumbed to the disease in the ICU and the definitive diagnosis was made on autopsy.

The diagnosis is often difficult to make because of the often vague clinical presentation and nonspecific radiographic findings. Histological identification of the fungus provides the definitive diagnosis, however cultures are often negative.4 A high degree of clinical suspicion is crucial for timely diagnosis and treatment.

References

A 40-year-old Woman with Chest Pain, ST Elevation, Elevated Troponin and Normal Coronary Arteries: A Case Report

Bhalaghuru Chokkalingam-Mani, MD and Avinash Chandra, MD

Electrocardiographic changes resembling myocardial ischemia or infarction can be caused by a variety of causes other than ischemia. One of them is acute myocarditis which further confounds clinical judgment by causing elevation in troponins as well. We report a case of myocarditis which underscores the importance of identifying the clinical presentation of acute myocarditis and the electrocardiographic changes that can be associated with it.

Case Report

A 40-year-old mother of two children with no significant past medical history presented to an outside hospital (OSH) complaining of intermittent chest pain for a week. She described it as “pressure-like” pain in the retrosternal and epigastric regions, with no radiation and reported it had been particularly worsening in the past two days. She notes that her youngest child aged three was sick with an upper respiratory infection in the past week. On arrival at the OSH, patient’s electrocardiogram (EKG) showed significant ST elevations in V1 and V2, ST depression and T wave inversion in the inferior and other precordial leads. (Figure 1) Her initial troponin was 28.6 ng/ml (normal range – less than 0.5 ng/ml). Anticoagulation was initiated with heparin and an emergent cardiac catheterization was performed at the OSH, which revealed normal coronary arteries.

During the procedure, she developed hemodynamic instability, requiring an infusion of norepinephrine and phenylephrine and a placement of an intra-aortic balloon pump (IABP). Patient was then transferred to our institution for further management. Subsequently, she started experiencing repeated episodes of sustained ventricular tachycardia, requiring multiple boluses and continuous infusions of amiodarone. She also developed an irregular tachyarrhythmia with right bundle branch block (Figure 2 and 3). Laboratory work and other cardiovascular studies from OSH were reviewed. Echocardiogram revealed an ejection fraction of 15-20% with severe global LV dysfunction. A presumptive diagnosis of acute myocarditis was made. On the second day of admission, extra-corporeal membrane oxygenation (ECMO) was initiated due to further hemodynamic deterioration.

Viral titers for adenovirus, cocksackie, Cytomegalovirus (CMV), herpes, echovirus, Epstein-Barr virus, hepatitis, para-influenza and varicella were sent. Antibody titers for Lyme, mycoplasma and toxoplasma were also sent. The titers were positive only

Figure 1. EKG 1 at the time of initial presentation to the OSH. EKG shows sinus tachycardia with ST elevation in V1 and V2, ST depression in V3 to V6, I, II, III, aVF.
for CMV. Methylprednisolone was administered intravenously at a dose of 1 gram daily for three consecutive days. Patient subsequently received a left ventricular assist device (LVAD). An endomyocardial biopsy revealed lymphocytic myocarditis. The Heart Failure service initiated a work-up for cardiac transplantation. Despite full mechanical circulatory support and multiple intravenous inotropic agents, the patient succumbed to her illness, a week after the transfer to our institution.

Discussion

Myocarditis is defined as myocardial inflammation in the absence of ischemia or infarction. It can present with minimal symptoms with slowly progressive cardiomyopathy or acute cardiogenic shock. Myocarditis can be caused by infectious and non-infectious causes. Viruses are the most common infectious cause, but bacterial and protozoal infections are also responsible. Non-infectious causes include rheumatological conditions and drug induced reactions. Depending on the acuity of clinical presentation, EKG changes and lab tests can provide clues to suspect myocarditis. Cardiac MRI is increasingly being used in suspected myocarditis cases but endomyocardial biopsy remains the gold standard for diagnosis. Viral titers may help in identifying a presumptive source but will usually not alter treatment. The mainstay of therapy is supportive care and a heart failure regimen should be initiated at the earliest time possible. If medical therapy fails, mechanical circulatory support can be considered. Some patients may eventually require a cardiac transplant.

We are conditioned to think that ST segment elevation indicates underlying coronary artery disease. While coronary artery disease resulting in acute coronary syndrome is one of the most important causes of ST segment elevation, it is crucial to remember that it can also be caused by many other conditions viz., left bundle branch block, early repolarization, myocarditis, pericarditis, etc. Myocarditis can cause a spectrum of EKG changes that include ST segment elevation, ST depression, any degree of heart block, T wave inversion, abnormal Q waves, bundle branch blocks, atrial and ventricular arrhythmias. Numerous cases of myocarditis mimicking myocardial infarction have been reported. However, in myocarditis the ST elevation does not correspond to any coronary artery distribution and ST depressions while present are usually not reciprocal. These can serve as distinguishing features between myocarditis and an infarct. But, unfortunately, EKG changes are non-specific and in cases with focal myocarditis, they can closely resemble an acute myocardial infarction. Consequently, recognizing acute myocarditis remains a serious challenge and inappropriate management of the disease can lead to fatal consequences.

In acute myocarditis, elevation of troponin can also be misleading. Elevated troponins can occur in any condition that causes myocardial damage and does not necessarily imply coronary artery disease. Even though the cause of troponin elevation is significant myocardial injury as in the present case, it is crucial to always assess EKG changes and troponin elevation, with respect to the clinical presentation. This case highlights the importance of understanding the pathological
process of EKG changes and troponin elevation and the possible clinical challenges that arise, when faced with a combination of these abnormalities.

References


Figure 3. EKG 3 was obtained on hospital day 2. Sinus tachycardia with right bundle branch block and left anterior fascicular block. There are frequent PVCs which preempt AV nodal conduction resulting in shorter PR intervals. Note the QRS duration nearly 260 milliseconds indicating severe myocardial injury in addition to the bundle and fascicular blocks.
A Rare Case of Abacavir Hypersensitivity Syndrome
Charles-Lwanga Bennin, MD

Case
A 56-year-old African American male with a history of type II diabetes mellitus complicated by neuropathy, infections with human immunodeficiency virus (HIV), with a known CD4 count of 25 per cubic millimeter, hepatitis B and hepatitis C presented with six(0,8),(996,995)(197,8),(802,921)months of generalized weakness over his lower extremities, poor balance, nausea and vomiting. The patient had recently started anti-retroviral therapy (ART) and noticed that the onset of his symptoms coincided with the initiation of this therapy. He was taking Trizivir, which consists of abacavir (300mg each day), lamivudine (150mg each day), and zidovudine (300mg each day), atazanavir (300mg each day) and ritonavir (100mg each day). The patient was also taking trimethoprim/sulfamethoxazole (TMP-STX) and fluconazole as prophylaxis against opportunistic infections. He described his generalized weakness as musculoskeletal and involving all his extremities, especially his legs: it was exacerbated with activity and relieved with rest. This weakness had led to gait instability without falls. He noted that his nausea was constant and had resulted in non-bilious, non-bloody emesis. He vomited approximately 2-3 times per day for 3 days. As a result, he had poor oral intake. He denied any fevers but he did report chills. He also reported a 40-lb weight loss over 3 months. Of note, he noticed that his symptoms diminished when he stopped taking of his ART medications. As a result, the patient had been non-compliant with his ART. He denied any significant alcohol consumption or recreational drugs use.

On examination, the patient was febrile to 100.4 degrees Fahrenheit, tachycardic to 104 beats per minute, and mildly hypertensive to 138/79. He had no lymphadenopathy; his cardiovascular exam was tachycardic but otherwise within normal limits; and his pulmonary exam revealed basilar crackles. His abdominal exam was unremarkable. The patient’s neurologic exam revealed no cranial nerve deficits or ataxic gait. Strength was preserved in all extremities with no sensory deficits. On admission, his laboratory work up (Table 1) was significant for normocytic anemia, leukocytosis, hyperkalemia, hyponatremia and elevated creatinine.

Hospital Course
The patient was diagnosed with probable abacavir hypersensitivity. This was a clinical diagnosis in the setting of a negative infectious workup. His ART was discontinued. The patient was tested for the HLA-B*5701 allele. This allele, which has an association with abacavir hypersensitivity, was negative in the patient. Over the following thirty six hours his complaints gradually improved. He regained his strength and had complete resolution of his nausea and vomiting before discharge.

Discussion
Abacavir is a nucleoside reverse transcriptase inhibitor used as part of the ART regimen in treating patients with HIV. It has been in use since 1998. Abacavir is an important guanosine analog that targets reverse transcriptase with high bioavailability and the ability to cross the blood brain barrier. Its use as a once daily medication helps encourage compliance among patients.

Abacavir hypersensitivity syndrome (HRS) is a sub-type of drug hypersensitivity syndrome. The syndrome is an idiosyncratic reaction with a delayed onset that can be fatal. The symptoms associated with abacavir hypersensitivity syndrome result from an immunologically mediated hypersensitivity reaction involving the major histocompatibility complex class I allele HLA-B*5701. An overriding theory involves abacavir stimulating antigen specific HLA-B*5701 restricted CD8+ T Cells. For other drugs, hypersensitivity syndrome may occur as the result of genetic deficiency of a detoxifying enzyme,

Table 1. Admission Laboratory Values and Reference Range in Adults (Righthand column)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>12.9 K/mm³</td>
<td>3.6 – 10.6</td>
</tr>
<tr>
<td>RBC</td>
<td>2.75 M/mm³</td>
<td>4.70 – 5.43</td>
</tr>
<tr>
<td>HGB</td>
<td>8.4 gm/dl</td>
<td>12.3 – 16.3</td>
</tr>
<tr>
<td>HCT</td>
<td>23.8 %</td>
<td>35.5 – 52</td>
</tr>
<tr>
<td>MCV</td>
<td>86.6 FL</td>
<td>82.7 – 97.7</td>
</tr>
<tr>
<td>RDW</td>
<td>15.0 %</td>
<td>11.5 – 16.5</td>
</tr>
<tr>
<td>PLT</td>
<td>267 K/mm³</td>
<td>150 – 430</td>
</tr>
<tr>
<td>MPV</td>
<td>8.6 fl</td>
<td>6.2 – 10.0</td>
</tr>
<tr>
<td>CD4+</td>
<td>25 Cells/uL</td>
<td>594 – 1663</td>
</tr>
<tr>
<td>CD8+</td>
<td>301 Cells/uL</td>
<td>272 – 932</td>
</tr>
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</table>
drug immunosuppression, drug-specific T cell or viral drug interactions. This hypersensitivity reaction can occur up to six weeks after initiation of therapy.

Abacavir hypersensitivity syndrome is characterized by gastrointestinal symptoms including nausea, vomiting, abdominal cramping, respiratory symptoms including coughing and shortness of breath and constitutional symptoms including fever, body rash and weight loss. Some studies have also linked abacavir to an increased risk of myocardial infarction. Abacavir HRS is a clinical diagnosis but there are tests that support the diagnosis. Along with an assay for the HLA-B*5701 allele, epicutaneous patch testing may be utilized. The method involves the application of antigen to the skin at standardized concentrations to the back or limbs. The ideal timing of the patch test readings is on day 2 and day 4, with additional reading at day 6 or 7 which will pick up approximately 10% more positives that were negative at days 2 and 4. This patch will produce both a visible response along with palpable skin changes. Studies have shown that all patients with abacavir HRS and a positive skin test all carry the HLA-B*5701 allele, however not all HLA-B*5701 allele carrying patients will have abacavir HRS. It is also important to note that while a positive epicutaneous patch testing confirms abacavir HRS, a negative result cannot rule out HRS. Abacavir HRS is often over diagnosed in African Americans; a low frequency of African Americans carry the HLA-B*5701 allele.

Treatment of abacavir HRS involves stopping administration of abacavir. It is important not to re-challenge a patient with a positive clinical reaction as there is the possibility of increased morbidity and death. Avoiding abacavir in patients with HLA-B*5701 has been shown to reduce the incidence of this hypersensitivity syndrome. Although ART regimen initiation should be left to infectious disease specialists, it is important to be aware of the recommendations by the FDA pertaining to abacavir HRS (Summarized in Table 2).

References

<table>
<thead>
<tr>
<th>Table 2. Abacavir Hypersensitivity Treatment Recommendations, adapted from the Federal Drug Administration guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for the HLA-B*5701 allele is recommended for all patients prior to starting abacavir therapy.</td>
</tr>
<tr>
<td>Screening is recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.</td>
</tr>
<tr>
<td>For HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be considered only under exceptional circumstances when the potential benefit outweighs the risk.</td>
</tr>
<tr>
<td>HLA-B<em>5701-negative patients may develop a hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B</em>5701-positive patients.</td>
</tr>
<tr>
<td>Discontinue abacavir therapy permanently if the patient becomes seriously ill and hypersensitivity cannot be ruled out, regardless of HLA-B*5701 status.</td>
</tr>
<tr>
<td>Following a hypersensitivity reaction to abacavir, NEVER restart abacavir or any abacavir-containing product because severe symptoms can occur within hours and may include life-threatening hypotension and death.</td>
</tr>
</tbody>
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Primary Cutaneous Nocardiosis in a Heart Transplant Patient: A Case Report
Kiran Devaraj, MD, Joanna Rodriguez, MD, Bryan Hess, MD and Paul Mather, MD

Case
A 38-year-old female with history of longstanding non-ischemic cardiomyopathy underwent orthotopic heart transplantation (OHT). Her past medical history was significant for factor V leiden and methylenetetrahydrofolate reductase (MTHFR) heterozygous deficiencies with chronic pulmonary embolism, sickle cell trait, atrial flutter, type 2 diabetes mellitus, and hypertension. The patient had a long and complicated course post-transplantation. Immediately after OHT, she was noted to have donor-specific human leukocyte antigen (HLA) antibodies treated with 5 cycles of plasmapheresis. On further biopsies it was noted that she had acute cellular rejection requiring pulse-dose parenteral steroids on multiple occasions. Her immunosuppression therapy consisted of tacrolimus, mycophenolate and prednisone. Six months post-transplant she was noted to have a spontaneous 4cm right calf muscle hematoma based on lower extremity ultrasound that was felt to be due to her underlying hematologic disease. At 7 months post-transplant the patient was hospitalized twice. The first admission was for multifocal necrotizing pneumonia. Although sputum cultures were non-diagnostic, the patient improved with 2 weeks of antibiotic treatment. The second admission occurred after a routine right heart catheterization that showed hemodynamic parameters concerning for rejection. At that time, the patient received empiric parenteral pulse steroids while waiting for final pathology results; these were negative for rejection and the patient’s immunosuppressants were continued at previous doses.

The newest hospitalization was 8 months post-transplant, when she was admitted with a chief complaint of worsened right-sided calf pain for a month. On physical exam the patient was noticed to have an area of warmth, induration and palpable tenderness. Patient denied any other symptoms, and specifically denied fevers, chills, respiratory symptoms or trauma. Imaging studies on admission included a lower extremity ultrasound that showed the hematoma had increased in size to 9 cm from previous study 2 months prior. Lab studies to assess any acute hematologic cause of recurrent spontaneous hematoma were negative. The differential diagnosis on admission included a leg abscess; however the absence of fever, leukocytosis and loculations made it seem unlikely. A calf MRI performed 4 days later showed the collection had increased to 13 cm. It was complex but still compatible with hematoma, although superimposed infection could not be ruled out. At this point it was decided for the patient to undergo an ultrasound guided fluid aspiration for diagnostic and therapeutic purpose, given the patient’s continuing pain and rate of growth. Fluid aspiration yielded 50 cc of pus. Broad spectrum antibiotics were started, and that evening the patient went to the operating room for an incision and drainage. The following day the wound culture grew a modified acid fast gram positive bacilli (by modified Kinyoun method) that immediately raised the concern for infection with nocardia species, especially given patient’s immunosuppression and recent treatment with pulse-dose parenteral steroids. Patient’s antibiotics were narrowed to intravenous ceftriaxone and patient was discharged home on this regimen, to convert to oral trimethoprim-sulfamethoxazole (TMP-SMX) 4 weeks later for at least a 6

Figure 1. Gram stain from our patient showing gram positive bacilli bacilli.

Figure 2. Modified Acid Fast (Kinyoun) Stain showing acid fast bacilli
month course. Final DNA sequencing results of the organism confirmed the diagnosis of Nocardia cyriacigeorgica.

Discussion

Nocardia bacteria are weakly acid-fast (by modified Kinyoun, Ziehl-Neelsen, and Fite-Faraco methods) gram positive bacilli that grow slowly in aerobic culture. Nocardia species are saprophytes that are found worldwide in soil. There are various nocardia species that cause human disease, most commonly N. brasiliensis, N. otitidiscaviarum, N. farcinica, N. nova, N. transvalensis, and N. pseudobrasiliensis. Our patient’s pathogen, N. cyriacigeorgica, is the most common cause of nocardiosis in the southern United States. Nocardia infections are rare among the general population of the United States, with an approximate incidence of 0.35-4 cases per 100000 people. Infections are concentrated to people with depressed cellular-mediated immunity, including patients with HIV, solid organ transplants, bone marrow transplants, cancer, and rheumatologic disease on immunosuppressive medications. In these patients, nocardia infections can have significant mortality, described as 11-67% (in case series with sample sizes of greater than or equal to 10). Nocardia infections most commonly affect the lungs, central nervous system (CNS) system and skin. Nocardia pneumonia has a tendency for nodularity, cavitation and empyema. One half of patients present with extrapulmonary disease. CNS disease is most commonly an abscess. Therefore, patients with Nocardia skin infections may have primary cutaneous infection, or may have disseminated infection. Among immunocompetent persons, there are case reports of primary cutaneous infection. Primary nocardia skin and soft tissue infections are divided into three main categories: mycetomas, lymphocutaneous nocardiosis and primary cutaneous nocardiosis. Some form of traumatic skin opening classically precedes all three types, although iatrogenic cases have been reported. In tropical countries where mycetomas (Madura foot) are highly prevalent, nocardia is an alternative cause (after the more common fungal pathogens), resulting in non-painful chronic supplicative infection with draining sinuses and discharging granules. Primary cutaneous nocardiosis may include soft-tissue abscess, cellulitis, bulla or ulcer, but is classically acute and painful. Lymphocutaneous nocardiosis consists of an acute primary cellulitis with lymphangitic spread and causes lymphadenitis.

Medical treatment of cutaneous nocardia infections is largely empiric and based on experience with treatment of invasive disease. Historically, oral TMP-SMX has been used for treatment of nocardiosis, with minocycline as an alternative. Given the high mortality of serious or invasive infections, an empiric regimen of TMP-SMX, amikacin, and ceftriaxone or imipenem is recommended. Of note, more recent data suggests growing TMP-SMX resistance. Treatment in our patient was difficult given her chronic kidney disease and nephrotoxic immunosuppressive medication; therefore we empirically treated her with ceftriaxone and TMP-SMX alone.

Particularly in the heart transplant population, primary cutaneous nocardiosis remains a rare disease, with our online literature search yielding only three reported cases. All the three cases had an identifiable cause: cardiac catheterization, intramuscular injections, and an insect bite. Our patient had no such identifiable cause, either iatrogenic or traumatic.

In conclusion, nocardiosis is a rare but deadly disease that mainly affects immunocompromised patients. Cutaneous nocardiosis results from traumatic invasion and has three different manifestations, with the primary cutaneous and lymphocutaneous versions common in the developed world. Treatment with TMP-SMX is often overlapped with intravenous antibiotics for serious infections.

References

GI Dysmotility: A Case Report

Katie Osley, MD and Yiu Tak Leung, MD, PhD

Case Report

A 75-year-old male, with a medical history of diabetes, hypertension, coronary artery disease, status post coronary artery bypass graft, and left-sided breast cancer, status post left breast mastectomy, was transferred from an outside hospital with complaints of a month of constipation, nausea and vomiting. The patient presented to an OSH a month prior with recent onset of constipation, with no bowel movements for 10 days, changed from his usual habit of daily bowel movements. He initially responded to lactulose with a bowel movement and was discharged on a regimen of stool softeners and laxatives; however, upon returning home, he was again unable to move his bowels despite his bowel regimen and developed diffuse abdominal pain, nausea and vomiting secondary to distension. An outpatient esophagogastroduodenoscopy (EGD) showed that the patient had a normal esophagus and a large amount of retained food in the stomach, concerning for gastroparesis. This finding was thought to be secondary to his diabetes, despite his well-controlled blood sugars and a hemoglobin A1c of 7.0%. After two further weeks of constipation, the patient was readmitted to the OSH with abdominal pain, intractable nausea and vomiting, as well as a 20-25 lbs weight loss since his symptoms began. Imaging showed colonic gaseous distention, with the cecum dilated to 9.5 cm, and an un-prepped sigmoidoscopy was performed, showing no inflammation, polyps or masses; of note, a screening colonoscopy done 4 months prior identified and removed multiple benign polyps. A CT scan of his abdomen and pelvis also did not show any obstructing colonic masses. He was presumed to have colonic pseudo-obstruction, or Ogilvie Syndrome. Erythromycin was started without effect. He was subsequently given neostigmine, which was also unsuccessful in relieving his symptoms. The patient was then referred to another OSH for further workup. A 4-day gut motility study showed a pan-GI dysmotility disorder. Furthermore, a gastric emptying study revealed markedly delayed gastric emptying of both solid and liquid foods, but defecography was entirely normal. Non-contrast CTs of the chest, abdomen and pelvis again did not identify any masses or bowel obstruction, but did show enlarged precardial lymph nodes and prostatomegaly, as well as small thyroid nodules bilaterally. As the patient continued to fail to have a bowel movement and could not tolerate a diet, he was started on total parenteral nutrition and was transferred to Thomas Jefferson University Hospital (TJUH) for further evaluation.

On presentation to TJUH, the patient complained of occasional diffuse abdominal pain and distention, as well as nausea. He had not had any vomiting since he stopped eating when he was started on TPN. He denied any swallowing difficulty but did complain of constantly spitting up clear sputum. He had not had a bowel movement in more than 4 weeks since his initial response to lactulose at the first OSH. He had lost 30 lbs in the 4 weeks since his symptoms began. His review of systems was otherwise negative.

As noted previously, the patient’s medical history is significant for hypertension, hyperlipidemia, coronary artery disease status post coronary artery bypass graft 15 years ago, well-controlled type 2 diabetes diagnosed 8 years ago and benign prostate hypertrophy. He also had left-sided breast cancer 7 years ago, treated with a left mastectomy and a 5-year course of tamoxifen. Social history indicated no current abuse of alcohol, tobacco, or illegal drugs, though he admitted to a 20-pack-year smoking history, having quit 35 years ago. He is a long time employee of a steel company and also owns a farm in eastern Pennsylvania. Family history is significant for breast cancer in his sister and stomach cancer in his mother.

The patient’s admission labs were unremarkable, with a normal complete blood count, prothrombin time, partial thromboplastin time, basic metabolic panel and electrolytes. His thyroid function tests were also within normal limits. He did have an elevated prostate specific antigen of 11.6 ng/mL. On physical examination, the patient was afebrile with normal vital signs. He was alert and oriented to person, place and time, and in no distress. Of note, he had post-CABG median sternotomy scar that was well healed, as well as a left-sided scar on his left chest remnant of a mastectomy. His abdomen was soft with active bowel sounds, but diffusely distended and diffusely tender to palpation, without guarding or rebound. The remainder of his exam was otherwise benign.

Hospital Course

The patient was admitted for workup of his GI dysmotility. Initial imaging with an obstruction series again showed no evidence of an intestinal obstruction. A subsequent CT of the abdomen and pelvis demonstrated a normally appearing small and large bowel and identified no cause of his symptoms. He then underwent an EGD, which found esophagitis at the level of his gastroesophageal junction; however, the remainder of his esophagus appearing normal. His stomach had retained fluid and food in the fundus despite having not eaten for almost 2 weeks. The remainder of his stomach exam was remarkable for a spastic pylorus, which was treated with botox injection. There was no improvement in the patient’s gastric motility, however, and his symptoms of nausea, abdominal fullness and constipation persisted.

The patient was seen by the Neurology Service to evaluate the possibility of autonomic dysfunction as the etiology of his GI dysmotility. He was found to have orthostatic hypotension with a supine blood pressure of 182/80 mmHg and heart rate of 121 beats per minute and an upright blood pressure of 122/65 mmHg.
with a heart rate in the 180s beats per minute. Though the patient had previously been given a trial of neostigmine at the OSH, he was empirically started on pyridostigmine 60 mg three times a day. He received 5 days total of pyridostigmine, without relief of his constipation. The medication was promptly stopped on the fifth day when daily monitoring EKG showed development of first-degree heart block and bradycardia. EKGs following the cessation of pyridostigmine showed improvement of his PR interval and resolution of his bradycardia. Acetylcholine receptor binding antibody was checked and returned as normal. To further evaluate for autonomic GI dysmotility, a ganglionic acetylcholine receptor binding antibody titer was sent, which was also negative.

The Rheumatology Service was consulted regarding the possibility of an autoimmune etiology, such as systemic sclerosis, causing his GI dysmotility. The patient’s antinuclear antibody titer was positive, with a titer of 1:320 and a speckled pattern; however, the rest of his rheumatologic serologies, including anti-double stranded DNA, anti-sm, anti-RNP, Sjogren’s anti-SCL 70, anti-centromere and rheumatoid factor, were negative. Therefore, it was deemed very unlikely that his GI dysmotility was secondary to an autoimmune process. The possibility of infiltrative diseases, such as amyloidosis, causing his GI dysmotility was also examined; however, his serum and urine protein electrophoreses were both negative. Environmental exposures were also explored, given the patient’s social history of living on a farm. Lyme antibody and a heavy metal drug screen were negative.

There was significant suspicion that the patient’s GI dysmotility may be secondary to a paraneoplastic syndrome. Accordingly, he was evaluated with a serum paraneoplastic panel. This screen was positive for the anti-Hu (ANNA-1) antibody, which is associated with small cell lung cancer, prostate, and breast cancer. Though CT scans of the patient’s chest, abdomen and pelvis were negative for any masses, some enlarged precarinal lymph nodes and an enlarged prostate were noted. Given the patient’s history of breast cancer, as well as elevated PSA (11.6 ng/mL) and a remote smoking history, the patient was recommended to get an outpatient positron emission tomogram (PET) scan to workup any possible occult malignancy. He was also recommended to have biopsies done of his precarinal lymph nodes and his prostate, regardless of the PET findings. The patient was started empirically on intravenous steroids, along with lubiprostone to increase GI secretions. Approximately 5 days after being started on methylprednisolone 40 mg daily, and lubiprostone 24 mg twice a day, he was able to move his bowels, with a total of 4 bowel movements that day, suggesting that his symptoms were secondary a paraneoplastic syndrome from an occult malignancy. Though the patient did not continue to have bowel movements on the steroids and was still unable to tolerate a solid diet, he was discharged home with oral steroids and on a full liquids diet in order to facilitate the completion of an outpatient PET scan to screen for the highly-suspected occult malignancy.

**Background/Epidemiology**

Intestinal dysmotility has long been recognized as a paraneoplastic syndrome in small cell carcinoma of the lung (Ahmed and Schuffler). In 1991, Lennon et al. first recognized the association of gastrointestinal dysmotility and ANNA-1.

**Clinical Characteristics/Differential Diagnosis/Serological Testing And Other Studies**

The presence of ANNA-1 (or anti-Hu) can produce a variety of different clinical presentations depending on which part of the gastrointestinal tract is affected. Pseudo-achalasia, gastroparesis and intestinal pseudo-obstruction have all been linked to the autoantibody anti-Hu. The autoantibodies found in patients with paraneoplastic GI dysmotility are different from those thought to be responsible for primary achalasia in that the former may affect neurons throughout the GI tract. Therefore, many patients have a pan-dysmotility, although usually one of the above disorders will present as the predominant symptom. Gastroparesis is the most common presentation of GI dysmotility secondary to ANNA-1 antibodies and has been reported to resolve completely upon resection of associated tumors. These patients present with a marked delay of gastric emptying in the absence of gastric outlet obstruction. This produces symptoms of nausea, vomiting, early satiety, epigastric fullness and retained food in the stomach. On the other hand, patients with ANNA-1-induced pseudo-obstruction will present with either recurrent or persistent symptoms of bowel obstruction. Chronic neurogenic intestinal pseudo-obstruction is defined as severe impairment of intestinal motility producing symptoms of mechanical obstruction in the absence of any organic obstacle to intestinal transit. An obstructive etiology was ruled out in our patient via obstructive series films, CT of the abdomen and pelvis, and colonoscopy.

The diagnosis of paraneoplastic GI dysmotility requires a high index of suspicion. There are many alternative diagnoses that need to be considered during the work-up of achalasia, gastroparesis and chronic pseudo-obstruction. The differential diagnosis of gastrointestinal neuropathies associated with motor dysfunction include developmental, degenerative (idiopathic, paraneoplastic and infectious), toxic or drug induced, or systemic disease related (diabetes mellitus, scleroderma, amyloidosis) neuropathies. Cytomegalovirus, herpes simplex virus and trypanosome cruzi (Chaga’s disease) are the infections most often associated with degenerative inflammatory neuropathies. In our case, an investigation for infectious etiologies was negative including CMV PCR and stool studies. The patient remained afebrile and never had an elevated white blood cell count throughout the hospital course. A heavy metal drug screen came back negative and a thorough review of our patient’s medications failed to find a culprit. Negative serum and urine protein electrophoresis studies and a hemoglobin A1c
of 7% helped to rule out infiltrative processes and a diabetic autonomic neuropathy, respectively.

Paraneoplastic gastrointestinal dysmotility can be attributed to the recognition of the RNA binding protein, Hu, by anti-neuronal nuclear antibody (ANNA-1). These autoantibodies are thought to target tumor antigens that show cross-reactivity with myenteric neurons. Small cell lung carcinoma and thymoma are the most common neoplasms associated with paraneoplastic intestinal dysmotility due to ANNA-1 or anti-Hu antibodies. However, association with lymphomas and tumors of the breast, prostate and ovary have also been reported.

Lee et al. published a case series of patients with paraneoplastic GI motor dysfunction and found that small cell carcinoma of the lung (SCLC) presented an average of 8.7 months after the onset of GI symptoms in ANNA-1 positive individuals. This is opposed to the other associated malignancies (lymphoma, anaplastic lung adenocarcinoma and ovarian cancer) in which GI symptoms began an average of 14 months after the tumor was diagnosed. Of note, the latter individuals were seropositive for PCA-1 or N-type calcium antibodies rather than ANNA-1. In the same study, it was shown that 83% of the cases involved a second manifestation of a paraneoplastic disorder, including sympathetic and/or parasympathetic failure, peripheral sensorimotor neuropathy, syndrome of inappropriate anti-diuretic hormone, or cerebellar degeneration. Therefore, the presence of a neurologic disorder combined with a GI dysmotility may lead the clinician to search for underlying malignant causes. Our patient presented with asymptomatic orthostatic hypotension, which provided a clue that led our team to investigate neurologic causes of gastroparesis and pseudo-obstruction.

Breast tumors have rarely been associated with paraneoplastic GI dysmotility. One patient with bilateral breast cancer, which was treated with chemotherapy, achieved improvement of her concomitant gastroparesis as her tumor went into remission. The patient was presumed to have a paraneoplastic cause of her GI dysmotility and Berghmans et al. hypothesized that auto-antibodies were responsible due to the lack of mechanical obstruction and close clinical correlation. Our patient’s past medical history of the breast carcinoma prompted us to wonder if his clinical anti-Hu syndrome was a manifestation of his tumor recurrence. This is further supported by reports that gastrointestinal paresis and intestinal pseudo-obstruction may be the first sign of a recurring thymoma.

Management (Cancer Workup) and Treatment

In 13% of patients with SCLC, an unrelated primary malignancy exists, most commonly renal cell carcinoma. This suggests that a work-up for SCLC should still be pursued despite the presence of an alternate primary tumor. Our patient had a remote history of a breast tumor for which he had a mastectomy and tamoxifen therapy. He also had an elevated PSA and 6.8 cm prostate on CT scan that led us to consult urology for prostate biopsy. However, the procedure could not be performed secondary to a urinary tract infection that complicated the patient’s hospital course. Despite the evidence for other sources of a paraneoplastic tumor, our clinical suspicion for a SCLC remained high.

Kashyap et al. suggests that serial CT of the chest every 6 months is one conservative management strategy if the initial CT is negative. A PET scan with biopsy of suspicious nodes is an alternative approach. Finally, if the clinical picture is highly suggestive of an occult malignancy despite a negative initial work-up, bronchoscopy or mediastinoscopy may be offered to the patient. In the case of our patient, his initial chest CT was negative except for a few enlarged precarinal lymph nodes. It was decided that a lymph node biopsy would be offered to the patient if the PET scan failed to show a source. PET scan will allow simultaneous investigation for a breast carcinoma, prostate tumor or an occult SCCL. Finally, a full thickness intestinal biopsy may aid in this diagnosis by demonstrating an inflammatory infiltrate of lymphocytes and plasma cells that inhabit the myenteric plexus and lead to destruction of neural elements. However, a tissue diagnosis is not always necessary when gastrointestinal dysmotility occurs in conjunction with the presence of a tumor and circulating autoantibodies. Therefore, we suggest that serologic and other non-invasive tests take place first before considering this procedure.

There is no standard of care for the treatment of antibody-associated GI dysmotility, due to the rarity of the disease and the difficulty measuring response to therapy. Many different regimens combining prokinetic agents, systemic steroid therapy and other immunosuppressants have been reported. Pulse doses of neostigmine (2 mg administered intravenously) led to peristalsis and relief of colonic distention in a patient with positive ANNA-1 with paraneoplastic encephalomyelitis and autonomic neuropathy. A steroid taper starting at 60 mg per day of methylprednisolone led to a remission of symptoms for one year in a patient with idiopathic mesenteric ganglionicitis. A regimen of pulse steroids using methylprednisolone 100mg IV for three days improved symptoms of intestinal subocclusion in another patient with positive ANNA-1. On the other hand, Lucchini et al. reported that 38 patients with positive ANNA-1 and gastrointestinal dysmotility failed to respond to adrenal corticosteroids, plasma exchange, intravenous immune globulin (IVIG) or cyclophosphamide. Our patient had a limited response to neostigmine, pyridostigmine and erythromycin. However, after starting lubiprostone and intravenous steroids our patient did have a bowel movement and was able to tolerate a full liquid diet. He was sent home on a taper of oral steroids, but relapsed a few weeks later, requiring another hospitalization for intractable nausea, vomiting and abdominal pain.

References

Case Reports


Photograph by Soham Vakil, MD
Chest Pain and Troponin Leak in a Healthy 38-Year-Old Female
Gunjan Shah, MD

A 38-year-old female with a medical history significant only for a cholecystectomy for cholelithiasis presented to an outside hospital with a one day history of sharp, non-radiating midsternal chest pain that began when she bent over to pick something up. She has associated light-headedness and dizziness when she stood up, as well as palpitations, diaphoresis, and a sense of throbbing in her left arm. The symptoms persisted at rest for one hour before the patient arrived at the outside hospital. She was found to be in new-onset atrial fibrillation with a rapid ventricular rate up to 160 beats per minute. A diltiazem infusion was started which resulted in a decrease of the heart rate to 100 beats per minute. Her first troponin was <0.05 ng/mL, but a subsequent troponin was 0.59 ng/mL, prompting the initiation of a heparin infusion for acute coronary syndrome. At this point, she was transferred to Thomas Jefferson University Hospital for further management. Her chest pain had resolved without any other medication, and she remained chest pain free through the rest of her hospital course. Of note, she admitted to using alcohol, tobacco, and cocaine two days prior to admission. Her only medication is a daily oral contraceptive pill.

Her initial vital signs on transfer were a temperature of 97.9 degrees Fahrenheit, blood pressure of 97/63 mm Hg, heart rate on 112 beats per min, which was irregularly irregular, and respiratory rate of 20 breaths per minute with an oxygen saturation of 98% on room air. Her physical exam was significant for an enlarged left palatine tonsil, irregular heart rate, and ecchymosis on her neck.

Initial laboratory studies included a white blood cell count of 12,000 /L, hemoglobin of 14.1 g/dL, platelet count of 269,000 /L, creatinine of 1.1 mg/dL, AST 48 IU/L, and ALT 41 IU/L. Her maximum troponin was 0.59 ng/mL.

Subsequently, her rhythm converted to sinus rhythm. Her EKG showed sinus tachycardia, but no ST-T changes concerning for myocardial ischemia or infarction.

A cardiac catheterization was done with images as shown below.

Questions: Select the one lettered answer that is BEST in each question.

1. What is the most likely cause of her elevated troponin?
   a. Myocardial Infarction
   b. Cocaine use
   c. Myocardial Bridging
   d. Atrial Fibrillation

2. What factor is the most likely determinant of clinical significance?
   a. Length of tunneled artery
   b. Degree of systolic narrowing
   c. Location of artery
   d. Width during diastole
3. What is the initial treatment of choice?
   a. Beta-blockade
   b. Coronary stenting
   c. Aspirin
   d. Surgical myotomy

Discussion

Myocardial bridging (MB) is a congenital condition in which the normally epicardial coronary artery is tunneled through the myocardium. Its clinical significance remains unclear, but various case reports have associated it with myocardial ischemia, myocardial infarction, arrhythmias, and sudden death. By autopsy, the prevalence ranges between 5.4 and 85%, while by coronary angiography, 0.5–29.4%. It most commonly affects the mid-portion of the left anterior descending artery (although there are a few case reports where it involves the right coronary artery.). The condition was first described by Reyman in 1737 and is characterized by systolic compression of the artery.

One proposed mechanism for myocardial bridging causing myocardial ischemia is its association with coronary vasospasm. Another theory relies on the amount of blood flow during systole and diastole in the coronary vessels. Stress and exercise can increase the body’s sympathetic activity leading to tachycardia-induced ischemia. Tachycardia shortens the diastolic filling time and increases the importance of systolic filling, which accounts for only 15% of coronary blood flow. Furthermore, atherosclerotic plaque typically forms in the artery proximal to the bridge, with relative sparing of the tunneled segment.

As resting EKGs are usually normal, other imaging modalities must be used to investigate the presence and significance of myocardial bridging. Coronary angiography is the gold standard with systolic compression of the tunneled segment portrayed as a “milking effect” and “step down–step up” phenomenon. Newer studies have been using other invasive imaging techniques such as intravascular ultrasound in which a “half-moon” phenomenon is seen or intracoronary Doppler ultrasound, in which a “fingertip phenomenon” or “spike-and-dome pattern is seen. Noninvasive imaging is possible with electron beam tomography multi-slice CT, magnetic resonance tomography, or transthoracic Doppler echocardiography, but the sensitivity and specificity preclude these from being the modalities of choice. Investigations have been conducted using myocardial perfusion imaging, and it has been found that the myocardial ischemia that results from bridging is associated more closely with the degree of systolic narrowing than with the length of tunneled artery or the location of MB.

Therapy for myocardial bridging concentrates on symptom management, with medical therapy being first line. Negative ionotropic and chronotropic agents such as beta-blockers and calcium-channel blockers increase the diastolic perfusion time, thereby decreasing compression of the coronary arteries. Nitrates are often avoided because they angiographically exacerbate myocardial bridging. Coronary stenting of the tunneled vessel and surgical myotomy are reserved for patients who fail medical management. With these modalities, long-term prognosis in patients with isolated myocardial bridging is generally good.

Answers: 1 – C, 2 – B, 3 – A

References
Case Report

A 41-year-old Thai female with past medical history of gastroesophageal reflux disease and duodenal ulcer who immigrated to the United States six years ago presented with a complaint of intermittent right upper quadrant (RUQ) pain for the last several years. Over the last year, she reported that the pain had significantly increased in intensity. She described the pain as crampy, beginning in the RUQ and radiating around to her back. There was no associated nausea, vomiting or weight loss. The patient had initially presented to an outside hospital a few months prior, was diagnosed with costochondritis, and was subsequently discharged. Her family promptly drove her to the emergency room of the outside hospital with severe abdominal pain and fevers. A computed tomography (CT) scan done in the emergency room showed a 4.6 cm x 2.8 cm x 4.9 cm multiloculated mass adjacent to the head of the pancreas along with several enlarged lymph nodes in close proximity to the mass. The patient was referred to an oncologist at a specialty cancer center where an endoscopic ultrasound (EUS) was performed. The EUS revealed a 5.1 cm x 2.2 cm hypoechoic, heterogeneous, septated lesion. Fine needle aspiration (FNA) was performed on the mass and cytology was sent to determine the etiology of the peripancreatic mass. The EUS-FNA cytology demonstrated necrotizing granulomatous inflammation, but special stains for tuberculosis and fungal etiologies were negative. Peripancreatic fluid, porta hepatis fluid and sputum cultures at this time were all negative.

On admission, the patient’s vital signs were stable. She was alert, awake, and oriented. She had a normal temperature on admission but became febrile to 102 F in the emergency room. Her heart and lung exam were within normal limits. On abdominal exam, she was found to have significant RUQ and epigastric tenderness, with no distention, rebound, or guarding. She had normally active bowel sounds with no palpable organomegaly. At presentation, her white blood cell count was slightly elevated at 11.1 x 10^3 /μL but the rest of her complete blood count panel and basic metabolic panel were within normal limits. Her amylase was 85 IU/L, and her lipase was 20 IU/L. Her hepatic function panel was within normal limits except for a slightly elevated alkaline phosphatase level at 108 IU/L.

After being transferred to Thomas Jefferson University Hospital, a chest CT and repeat abdominal CT and EUS were performed. The CT of the abdomen showed a multiloculated cystic mass in the porta hepatis, portacaval, and peripancreatic region measuring approximately 4.3 cm x 3.1 cm (Figure 1). Additionally, severe narrowing of the distal main portal vein and narrowing of the left portal vein from the adjacent mass were described. The porta hepatis component of the mass had slightly increased in size and demonstrated increased cystic changes and increased compression of the main portal vein and left portal vein in comparison to a CT done a month ago. The pancreas itself was not involved and appeared unremarkable, but had been displaced by the mass. No pancreatic ductal dilatation was observed.

Figure 1. Abdominal CT showing a multiloculated cystic mass in the porta hepatis, portacaval, and peripancreatic regions.

Figure 2. CT chest demonstrating bilateral upper lobe tree-in-bud opacities suggestive of infectious or inflammatory processes and endobronchial spread of infection.
Case Reports

The chest CT demonstrated bilateral upper-lobe “tree-in-bud” opacities suggestive of infectious or inflammatory processes including endobronchial spread of infection, such as seen with tuberculosis (TB) (Figure 2). The differential diagnosis also included other atypical mycobacterial organisms, viruses and fungal etiologies.

The repeat EUS described a 4.3 cm x 2.8 cm hypoechoic, lobular, homogeneous lesion present adjacent to the pancreatic head (Figure 3). The mass had a cystic component to it and compressed but did not invade the portal vein. The entire pancreas appeared normal with full visualization of the body and tail. Several 1 cm, oval, heterogeneous peri-pancreatic lymph nodes with poorly defined margins were also found. Examination of the fluid aspirated from the pancreatic lesions showed a collection of epithelioid histiocytes in a background of inflammatory cells and debris (Figure 4). Additionally, a cell block sample of the aspirate showed a classic granuloma with a multi-nucleated giant cell surrounded by epithelioid histiocytes in a background of lymphocytes and necrotic debris (Figure 5).

Staining of the fluid culture from the porta hepatis and peripancreatic masses were negative with specialty stains for acid-fast bacilli, but cultures eventually grew out mycobacterium tuberculosis (MTB) complex after 5 weeks. The state health department was notified. Follow up was arranged upon discharge for continuation of MTB treatment.

Discussion

MTB is an acid-fast bacillus that causes an infection known as tuberculosis. TB is characterized by chronic granulomas and had been a common disease of undeveloped countries decades ago, but has been well controlled with advancing antibiotic therapies more recently. Over the last few years however, there has been a rise in the incidence even in developed countries such as the United States due to increasing numbers of patients with immunocompromised states and due to increasing numbers of immigrants from areas with endemic TB.1,2,4,5,7 TB is a disease that can present almost anywhere in the body, but is most routinely discovered in the lungs. For example, TB of the digestive tract can occur anywhere from the esophagus to the anus. Additionally, tuberculosis can present as an abdominal infection, localizing in the liver, spleen, or ileocecal region resulting in non-specific findings such as fever, pain, malaise,
weakness, weight loss, anorexia, and jaundice.\textsuperscript{1,2,5,7} Pancreatic TB, is exceptionally rare with only a handful of cases having been published.\textsuperscript{1,3,5} The reasoning behind this is unclear, but it is hypothesized that digestive pancreatic enzymes interfere with the seeding of mycobacterium into the pancreatic tissue.\textsuperscript{4,7} Pancreatic TB currently is being diagnosed more frequently, partly because of the increase in immunodeficient patients and partly due to improved pancreatic imaging.

Pancreatic TB is often indistinguishable from pancreatic tumors on CT imaging because both present as non-specific lesions in the pancreas; FNA with cytology is needed to make a definitive diagnosis.\textsuperscript{1,3,4} Positron emission tomography (PET) scanning is typically used to differentiate cancerous lesions from other concerning processes, but is not useful with TB related lesions, which can cause an increased uptake on PET scans, notably in the lungs.\textsuperscript{6} Low-attenuation peripancreatic and periportal adenopathy with peripheral rim enhancement may support a diagnosis of pancreatic TB on CT.\textsuperscript{2} In an article by Xia, in which characteristics of pancreatic TB were elicited via 16 patients and 58 prior literature reports, some associations and possible ways to distinguish pancreatic TB from pancreatic tumor were identified. Xia found that young people and females were more likely to have pancreatic TB, whereas pancreatic cancer was more commonly found in males and the elderly. Moreover, it was found that not all people had a past history of TB, but most who develop pancreatic TB come from a region known to be endemic for TB. The most common symptoms that patients complained of were epigastric pain, fever, and weight loss, though these were not specific to pancreatic TB.\textsuperscript{1,3,7} Lastly, it was found that FNA with tissue cytology was the most definitive non-surgical way to diagnose pancreatic TB and rule out carcinoma.\textsuperscript{1,4,7}

The spread of TB to the pancreas is poorly understood, but may occur as one of a number of different forms of infection. It may come from generalized, or military TB, in which case MTB is the most common causative agent. Spread to the pancreas can occur as a result of seeding from celiac, retroperitoneal, or peripancreatic lymph nodes. In this case, \textit{Mycobacterium bovis} is likely the infectious agent.\textsuperscript{1,6,7} Also, spread to the pancreas may result from hematogenous dissemination of bacteria from the lungs.\textsuperscript{2,6} Lastly, a primary localized pancreatic TB may be seen. This is a very rare form of TB, which points to the intestinal tract as the root of infection.\textsuperscript{3,6}

\textbf{Conclusion}

Pancreatic TB is a rare but serious condition. The variability in imaging of pancreatic TB poses potential diagnostic problems. Pancreatic TB is curable with standard antibiotics if it is diagnosed early enough, but delay of diagnosis or misdiagnosis can potentially be fatal.\textsuperscript{2,3} In immunocompromised patients or young patients from areas endemic with TB in whom TB is clinically suspected, EUS-FNA should be performed in order to determine the etiology of the pancreatic lesion.\textsuperscript{4,5} The obtained sample should be sent for an acid-fast bacilli stain, as a preliminary test for mycobacterium species, even though the yield is low. Cultures should also be sent, though they can take up to six to eight weeks grow for definitive rule out.\textsuperscript{5} Patients should be started on antibiotics as soon as TB is clinically suspected. Often, they do very well with few lasting complications once treatment begins.

\textbf{References}

A 35-year-old Man with New Onset Blindness
Cecilia Kelly, MD, Claire Raab, MD and Aimee Lee, MSIV

Case Report

A 35 year-old homosexual male from Trinidad with no known past medical history presented with a complaint of new-onset blindness. He stated that his vision had become increasingly “dim” to the point that at presentation, he had minimal light perception in either eye. This decrease in vision had occurred over the course of a week. He denied any trauma, eye pain, headache, nausea or vomiting.

On review of systems, the patient reported bilateral lower extremity numbness and tingling as well as left lower extremity weakness that had been present for approximately six months. He attributed these neurologic symptoms to a car accident one-year prior. Over these six months, he was additionally complaining of intermittent night sweats and chills, patchy hair loss on his scalp, and facial acne. Further questioning revealed a history of unprotected anal intercourse with several male partners. He had not undergone any testing for sexually transmitted diseases in the past. He had not seen a doctor for over 10 years.

Physical examination was significant for patchy alopecia of the scalp, perioral ulcerating lesions, and four nonerythematous soft macular lesions, approximately 2 mm x 3 mm, on the left cheek and chin. Neurological examination revealed normal cranial nerves except for in the pupilary exam, which displayed small pupils bilaterally that were reactive to accommodation, but did not react when exposed to light. Strength was decreased to 4/5 in the right lower extremity in all muscle groups and 3/5 in the muscle groups of the left lower extremity, with an associated left-sided foot drop. Lower extremity reflexes were absent bilaterally.

Laboratory studies revealed a profound lymphopenia. A rapid human immunodeficiency virus (HIV) test was positive with western blot confirmation. CD4+ count was 40 cells/mm³. VDRL, RPR, and FTA-ABS (venereal disease research laboratory, rapid plasma reagin, fluorescent treponemal antibody absorption test; FTA-ABS respectively) were positive as well. With these neurological symptoms in the setting of a new diagnosis of acquired immunodeficiency syndrome (AIDS) and syphilis, lumbar puncture was performed to look for infection. The results of cerebrospinal fluid analysis showed an elevated protein level with a normal glucose, lymphocytic pleocytosis, and a reactive VDRL serology, findings that were all consistent with neurosyphilis.

Consequently, the patient was initiated on a 3 week course of intravenous penicillin G. He was able to recover partial vision; however his foot drop and numbness persisted, requiring the use of a cane for support with mobility.

Discussion

Syphilis is a treatable sexually transmitted infection caused by the spirochete Treponema pallidum. The natural history of this infection can be divided into early and late processes. Early syphilis includes primary, secondary, and latent infections. If left untreated, these can progress to tertiary syphilis, the late process of the disease which is no longer curable. Late syphilis occurs after a latent period of one to thirty years following initial infection.

Tertiary syphilis is characterized by cardiovascular, dermatologic, and neurologic involvement. Patients develop chronic inflammation of the thoracic aorta resulting in aortic dilation and aortic valve regurgitation. These manifestations can present as a murmur, usually that of aortic insufficiency, and can result in left-sided heart failure. Granuloma formations, known as gummas, are specific to syphilis and found in dermal, visceral, or bony areas. Our patient presented with gummas on his face that he mistook for acne (Figure 1). Gummas can present as ulcerating lesions on the skin or even as mass lesions. General paresis and personality changes progressing to dementia are also characteristic of neurologic syphilis. Syphilitic involvement of the central nervous system can cause damage to the posterior columns and dorsal roots of the spinal cord, known as the syndrome of tabes dorsalis. This involvement results in limb paresthesias, episodic nausea and vomiting, absent lower extremity reflexes, and decreased vibratory and positional awareness. On physical exam patients may present with the classic finding of Argyll-Robinson pupils, which refer to the condition where the pupils are able to accommodate but unable to constrict to light or painful stimuli. Other findings include dysarthria and intention tremors. Many of these clinical signs, including gummas, paresthesias, paresis, and Argyll-Robinson pupils, were seen in our patient.

Figure 1. Small rubbery gummatous lesions seen on the right cheek, chin, and lips in a patient with tertiary syphilis.
Before the use of antibiotics, tertiary syphilis occurred in 20–40% of all individuals that had been infected with the disease. In the United States, the Center for Disease Control and Prevention (CDC) reports that the rates of neurosyphilis ranged from 5.5-6.0 cases per 100,000 infected individuals in 2004. In 2007, primary and secondary syphilis prevalence in Philadelphia, Camden, and Wilmington areas was 3.5% with 205 new cases reported.

Neurosyphilis in HIV/AIDS patients has been recognized and reported since the beginning of the HIV/AIDS epidemic. Symptomatic neurosyphilis is a rare manifestation of syphilis in the United States, due to the near complete eradication in the 1940s following the introduction of penicillin. However, neurosyphilis began to appear again in the 1980s in patients infected with HIV. In the early 2000s, the incidence of neurosyphilis began to rise dramatically, primarily in men who have sex with men (MSM). The CDC conducted a review of these cases, reporting an estimated 1.7% risk of symptomatic early neurosyphilis in HIV-positive MSM, and an estimated 0.5% risk of persistent symptoms six months after treatment.

**Conclusion**

Because of the increasing incidence, clinicians should have a high index of suspicion for syphilis in HIV-positive MSM presenting with meningismus, or motor or sensory cranial nerve deficits. As seen in this case, the clinician must be sure to rule out HIV/AIDS in a MSM who is presenting with neurosyphilis.

**References**

Case

A 71-year-old woman, with a history of non-small cell lung cancer (NSCLC) with subsequent pneumonectomy presented with worsening dyspnea on exertion and non-productive cough. The patient first noted the shortness of breath and cough 4 weeks prior to presentation, which were refractory to albuterol nebulization. The patient also reported a 6 lb. weight loss during this time period. She denied fevers, chills, night sweats or chest pain. The patient was diagnosed with NSCLC 11 years ago and underwent a right-sided extrapleural pneumonectomy at that time. She received no radiation or chemotherapy. She did not require home oxygen and reported a generally good functional status prior to the development of her latest symptoms. Other past medical history included hyperlipidemia. The patient had been smoking a pack of cigarettes per day for the past 35 years, but denied alcohol or illicit drug use. Current medications included albuterol nebulizer, aspirin, alprazolam, levothyroxine, simvastatin, and over-the-counter Excedrin (acetaminophen, aspirin, caffeine).

On examination, the patient appeared in minimal respiratory distress. She was afebrile, blood pressure was 110/60 mm Hg, the pulse 97 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 95% on ambient air. Her heart exam had no murmurs, rubs, or gallops. There were coarse breath sounds over the lower field of the left lung and decreased breath sounds with egophony at the right base. There was no lower extremity edema or calf tenderness. White blood cell count was within normal limits without a bandemia. Chest radiography revealed opacification of the right hemithorax with overall volume loss and left-to-right mediastinal and tracheal shift in keeping with prior right pneumonectomy. There were several surgical clips seen in the right hemithorax. The left lung field was unremarkable without pneumothorax, pleural effusion, pulmonary edema or focal consolidation. The cardio-mediastinal silhouette evaluation was severely limited due to significant left-to-right mediastinal shift. The chest radiograph was interpreted by radiology as “stable post-pneumonectomy changes with no effusions, edema or consolidation.” A computed tomography scan was revealed hilar adenopathy with mass effect as well as a new 3 mm nodule in the left lower lobe.

A diagnosis of small cell cancer was made from bronchoscopy and subsequent tissue biopsy. A nuclear bone scan revealed no metastatic disease and the patient was treated with 3 doses of cisplatin and etoposide. She was discharged home in stable condition.

Discussion

Pneumonectomy is the surgical removal of a lung. It is indicated in several circumstances including for the removal of tumorous tissue, in occasional settings of traumatic injury, and historically in pulmonary tuberculosis. The removal of a lobe of the lung is termed lobectomy and the removal of a section of the lung is termed wedge resection. The first pneumonectomy dates back to the 1890s when William Macewen performed the procedure in multiple surgical stages.1 In 1933, the first single stage en block resection was accomplished by Graham and Singer. 2-5 Today, there are two surgical types of pneumonectomy performed. A simple pneumonectomy involves the removal of the affected lung only. An extrapleural pneumonectomy involves removal of the affected lung as well as partial resection of the ipsilateral diaphragm, parietal pleura and pericardium.

Predictable anatomical changes occur following pneumonectomy. These changes are especially important when physical findings deviate from the norm. Typically following pneumonectomy, the empty space is filled with air. This space gradually accumulates with fluid over weeks to months. The gradual resorption of air and replacement with fluid eliminates the need for a chest tube post-pneumonectomy.2 Complete opacification on chest radiograph eventually occurs in most patients, however a small fraction of patients with post-pneumonectomy will have residual air.5

In addition to the gradual accumulation of fluid, the post-pneumonectomy space shrinks, resulting in the elevation of the ipsilateral hemi-diaphragm, shifting of the mediastinum towards the post-pneumonectomy space, and hyperinflation and encroachment of the remaining lung into the post-pneumonectomy space (Figure 2 & 3).
Although uncommon, fluid can accumulate more rapidly during the first 3 days after surgery. When this occurs, hemothorax and chylothorax must be worked up and ruled out. Rapid post-pneumonectomy edema carries a high mortality rate of more than 50%.6

Pneumonectomy has predictable effects on the positions of other vital organs depending on which lung is removed. In a right pneumonectomy, elevation of the right hemi-diaphragm can result in an elevation of the liver into the right post-pneumonectomy space. The heart and great vessels eventually shift into the vacant right post-pneumonectomy space.7 These findings are evident on our patient’s imaging. In a left pneumonectomy, the heart rotates counterclockwise into the vacant left post-pneumonectomy space.8

In light of these anatomical changes, several complications can occur. One complication is a direct result of the severe shifting of the mediastinum, called “post-pneumonectomy syndrome.” The surgical incidence for post-pneumonectomy syndrome is 1 in 640 cases, with young age and female sex as strong risk factors.9-12 This phenomenon causes large airway obstruction due to the narrowing and stretching of the main bronchus. Symptoms typically present as progressive dyspnea, cough, inspiratory stridor, and recurrent pneumonia5. Another complication is the formation of bronchopleural fistulas. The incidence of bronchopleural fistulas associated with pneumonectomy is approximately 5% with a mortality of 16-23%.13 The frequency of bronchopleural fistulas is higher for right-sided pneumonectomies.5 Symptoms can present as fever, productive cough, hemoptysis, subcutaneous emphysema,

Figure 2. CT Chest; Note the heart shifts into the vacant right pleural space.

Figure 3. CT Chest; Note the left lung encroaching into the right pleural space.
and persistent air leak from a chest tube. Other complications of pneumonectomy include esophageal fistula, pulmonary edema, arrhythmias and intracardiac shunting. Chronic pneumonectomy complications include tumor recurrence and emphysema.

**Conclusion**

In our case, we present a patient with post-pneumonectomy changes with radiologic findings on imaging. Given her history of right pneumonectomy, these findings were consistent with post-pneumonectomy changes. Incidentally, the patient was also found to have concomitant small cell lung cancer. With an understanding of post-pneumonectomy changes, our patient was correctly diagnosed and appropriately treated. Performing unnecessary tests and procedures can carry an increased risk of mortality, thus it is important to be aware of post-surgical changes and their complications both on physical examination and imaging studies.

**References**


"Dahab, Egypt", photograph by Sameh Gaballa, MD
RARE GRAM-NEGATIVE SEPSIS IN A NON-VENTILATED NEUTROPENIC PATIENT WITH AML

Jay Sellers, MD and Paurush Shah, MD

Case Report

A 57-year-old man with history of hypertension, hyperlipidemia, and gout presented for evaluation of both a perioral infection and an infection in his right great toe from an injury on the beach at his shore house. The toe trauma was complicated by a massive hematoma and phlebitis, which required antibiotics. His primary care physician ordered basic laboratory studies that showed an anemia and thrombocytopenia. He was sent to a Hematology and Oncology specialist and subsequently directly admitted to Thomas Jefferson University Hospital for blood transfusion and further work-up. Upon further questioning, the patient admitted to chills starting 2 weeks prior to admission, elevated temperatures, rigors, dizziness, weakness, shortness of breath and a weight loss of about 16 pounds over 1 month. He denied prolonged bleeding or easy bruising, but did admit to recurrent upper respiratory infections.

On admission, the patient’s white blood cell count was 8.9 x10^3 /µL, hemoglobin was 4.1 g/dL, and platelets were 5,000 /µL. There was a lymphocytic predominance on the manual differential. On physical exam, the patient was in no acute distress. He was awake, alert and oriented to person, place, and time. Vitals signs at that time showed the patient to be afebrile at 99.5 F and tachycardic at 112 beats per minute, with a respiratory rate of 16 breaths per minute, a blood pressure of 155/90 mm Hg, and an oxygen saturation 100% on room air. The patient’s heart and lung exams were both unremarkable. The only significant finding on exam was edema and tenderness over the entire right great toe.

Following admission, the patient underwent a bone marrow biopsy that revealed acute myeloid leukemia (AML) with markedly decreased background maturing trilineage hematopoiesis. Upon discussion with the patient, his family, and the medical team, it was determined that the patient would be initiated on induction chemotherapy with 7 days of cytarabine (7+3). Initiation of the induction therapy however, was delayed due to the infection in his right great toe. Radiography and magnetic resonance imaging of the right 1st toe revealed extensive osteomyelitis involving the right 1st toe. Chemotherapy was initiated a week after amputation of the right 1st toe. Vascular surgery was promptly consulted and the patient underwent amputation of the right 1st toe. Chemotherapy was initiated a week after amputation to allow for a period of treatment of the Pseudomonas and wound healing prior to inducing further immunosuppression.

Before and during chemotherapy, the patient had intermittent fevers with a peak at 102 F. Blood and urine cultures were obtained with the fevers, but the cultures were sterile. It was deemed likely that the fevers were due to tumor burden, but cultures were continually sent with each elevated temperature as a precaution. The patient tolerated his 7+3 chemotherapy and required several packed red blood cell and platelet transfusions during his stay. He had been doing quite well after chemotherapy and was almost 1 month post-treatment when he developed severe rigors and had temperatures up to 103 F during a platelet transfusion. Blood cultures were again sent, though all blood cultures prior to that day had been negative. It was initially thought that antibodies to foreign material in the platelet transfusion that the patient was receiving caused the rigors.

During his second episode of rigors, the patient had episodes of desaturations to as low as 80% while on 6 L nasal cannula. His saturations improved with bronchodilators and increased oxygen therapy via a non-rebreather facemask. A computed tomographic scan of the chest revealed pulmonary infiltrates in bilateral lower lung segments with developing pleural effusions and mild pulmonary edema. The patient continued to have rigors and elevated temperatures despite initiation of broad-spectrum antibiotics and desaturated to an oxygen saturation percentage in the high 80s and low 90s. He was quickly transferred to the medical respiratory intensive care unit for further care and management. On the next day, blood cultures grew Acinetobacter baumannii that was pan-resistant to the patient’s current broad-spectrum antibiotic regimen of aztreonam, ciprofloxacin, tobramycin, and vancomycin. He was intubated for respiratory distress and started on vasopressors. His clinical picture continued to deteriorate, and on the morning of hospital day 30 he expired.

Discussion

Acute Myeloid Leukemia and Neutropenic Fever

AML is a hematologic cancer characterized by an elevated number of myeloid cells in the bone marrow. This disease often causes arrested maturation of hematopoietic cells, leading to anemia, thrombocytopenia, leukopenia with neutropenia specifically, and sometimes a leukocytosis with poorly functioning or diminished granulocytes. Patients initially present with symptoms of fatigue due to anemia, bleeding from thrombocytopenia, and infection or fever due to inadequately functioning white blood cells. Patients may also present with pallor, shortness of breath, or as in this patient’s presentation, with non-healing wounds. Additionally, leukemic cell abnormalities may affect a variety of other tissues and organs, causing various other organ-specific symptoms.

Diagnosis of AML is routinely done via bone marrow biopsy and examination of the aspirate under microscopy. Detection of at least 30% myeloblasts with round or irregular nuclei, little cytoplasm and the presence of cytoplasmic Auer rods...
Although this never appeared indurated or erythematous. Our patient had several risk factors for developing life-threatening infections. As a result, antifungals are typically added after the patient has obvious mucosal barrier breakdown. Vancomycin and linezolid are common initial therapies for patients with febrile neutropenia, unresponsiveness of cancer to chemotherapy, and use of peripheral or central venous catheters.

Gram-negative bacilli, particularly Pseudomonas aeruginosa, are the pathogens of particular concern. Monotherapy with beta-lactams, carbapenems, and 3rd generation cephalosporins are common initial therapies for patients with febrile neutropenia. Typically, gram-positive antimicrobial therapy is not empirically started at initial presentation, unless the patient has obvious mucosal barrier breakdown. Vancomycin and linezolid are common gram-positive antimicrobials prescribed in this setting. It is recommended however, that cessation of gram-positive coverage should occur if cultures remain negative for 72 hours. Fungal pathogens are also of concern, particularly after one to two weeks of neutropenia. Candida albicans is often implicated in central venous catheter infections, and Aspergillus species commonly cause invasive pneumonias, sinusitis, and skin ulcers. As a result, antifungals are typically added after the patient has had four or more days of neutropenia and fevers.

Our patient had several risk factors for developing life-threatening infection. He was functionally neutropenic on the day of admission, and remained profoundly neutropenic for his entire hospitalization, as his neutrophil percentage remained below 10% of the leukocyte differential. Additionally, he also had a peripherally inserted central catheter in his right upper extremity, although this never appeared indurated or erythematous. Our patient was also on all the appropriate antimicrobial therapies given the duration and severity of his neutropenia. On the day the patient developed rigors and positive blood cultures, he received aztreonam, caspofungin, ciprofloxacin, acyclovir, metronidazole, tobramycin, vancomycin, and voriconazole. Despite these broad-spectrum, potent combinations of antimicrobials, he still had fevers and eventually the positive blood cultures speciated out a strain of Acinetobacter baumannii that was highly resistant to all of the patient’s current antibiotics.

**Acinetobacter Baumannii:**

Acinetobacter species are aerobic, gram-negative bacilli commonly found in aquatic environments and in soil, and have become an increasingly important pathogen in nosocomial infections. Unfortunately, strains of acinetobacter are becoming increasingly resistant to common antimicrobials leading to a higher incidence in mortality. A 2005 study from Korea aimed to identify mortality risk factors in patients with Acinetobacter baumannii bacteremia. Their results identified an association with neutropenia as well as with an elevated Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The authors point to a mortality rate between 17%-52%. Additional studies have shown resistance patterns in Acinetobacter baumannii infections. In a 3-month study by Landman, et al. from Brooklyn, NY, it was found that 53% of the 419 strains isolated in 15 hospitals were resistant to meropenem and/or imipenem and of these, 12% were resistant to all standard antibiotics.

Given the multi-drug resistant patterns of Acinetobacter baumannii, it has been proposed that colistin may be one of the few antibiotics capable of combating these infections. Colistin, a polymyxin antibacterial, was first available for use in 1959. It is a bactericidal medication that binds to lipopolysaccharides and phospholipids in the outer cell membrane of gram-negative bacteria. This causes a disruption in the membrane leading to bacterial lysis and spillage of intracellular contents. Colistin fell out of favor in the 1980’s largely due to concerns of nephrotoxicity, neurotoxicity, and neuromuscular blockade. It has had a comeback of sorts recently due to demonstrated in-vitro bactericidal activity against gram-negative bacilli and relatively low resistance patterns. A small study from Brazil showed treatment with colistin resulted in a “good outcome,” defined by negative blood cultures, cessation of fever, and prevention of mortality for 35 out of 59 cases of Acinetobacter infections. This study does, however, report that 22 of the 59 patients died, although of unreported causes. One could argue that a “good outcome” is not an objective measurement and that no parameters were discussed regarding said outcome. Additionally, further quantification of so-called “good outcomes” should be clarified, especially when 22 of the patients in this small study died. Additionally, the authors describe an increase in the baseline serum creatinine in 32% of patients in the study due to colistin.
Conclusion

The complications of AML and neutropenia are a daily challenge to physicians caring for patients with this disease. The diseases itself, as well as all treatments for the disease predispose these patients to unique pathogens that can cause catastrophic harm or death. In an era of multi-drug resistant pathogens, clinicians must remain hyper vigilant for newly emerging resistance patterns and know how to combat these lethal microbes with appropriate antibiotics. If drug resistant bacteria are considered, swift action must be undertaken with aggressive antibiotics and potential infectious disease specialist consultation. Acinetobacter infections, although less common, have proven to be notoriously difficult to treat and potentially deadly.

Our patient in the intensive care unit did undergo a change in antibiotic coverage from aztreonam to meropenem, but he did not receive colistin. It is unlikely that using colistin would have helped given his clinical picture of profound gram-negative septic shock. Had our patient received colistin in the first hours of his rigors his outcome may have been different. Although it is impossible to predict, the astute clinician must always be aware of the multitude of resistant organisms and the arsenal of potential life-saving treatments against them. The challenge remains to develop new antimicrobials to keep up with the ever-changing patterns of bacterial disease.

References

Images in Clinical Medicine

Calciphylaxis
Darren Andrade, MD

A 51-year-old man with a history of end-stage renal disease on hemodialysis and diabetes mellitus presents with suprapubic pain and a worsening penile ulcer that he first noticed two months ago. What finally prompted the patient to go to the emergency department was the new symptom of urinary urgency—a symptom that concerned the patient as he had been anuric for five years. CT scan revealed calcification of the left pleura, vas deferens calcifications, and diffuse severe calcified atheromatous changes throughout the central and peripheral vasculature. These findings in combination with a painful ischemic necrotic penile ulcer strongly suggest the diagnosis of calciphylaxis. Due to the patient’s severe vascular insufficiency a skin biopsy has not been performed, as the wound will likely have difficulty healing after biopsy.

Figure 1. Painful ischemic necrotic penile ulcer

Chronic Tophaceous Gout
Sara Beltz, MD

Gout, existing since antiquity as “the king of diseases and the disease of kings,” can present as an acute gouty arthritis or as a chronic depositional arthropathy (chronic tophaceous gout). If left untreated, chronic tophaceous gout will develop in up to 30% of acute gout patients over 5 years. The prolonged hyperuricemia causes monosodium urate crystal deposition in the skin around the joints. Over time, this leads to painless nodular swellings on the extensor surfaces of any digit, the olecranon or prepatellar bursa, achilles tendon, or the helix of the ear. These tophi, usually 1-7mm, can have a chalky white discharge and may dissolve with treatment. Pain at the site of a tophus should be investigated by tapping the joint for fluid analysis and starting empiric antibiotics as these joints can become secondarily infected.

Figure 1. Nodular swellings from chronic tophaceous gout.
Digital Clubbing

Yiu Tak Leung, MD, PhD

This is a 66 year-old male with a history of cirrhosis who came into the office for a routine check-up and was noted to have “drumbstick fingers” or digital clubbing. Digital clubbing is a clinical sign most commonly associated with pulmonary diseases, such as lung cancer and interstitial lung disease, cyanotic heart disease and cirrhosis of the liver, but clubbing also may be idiopathic or congenital. Possible mechanisms include dilation of peripheral vessels and secretion of growth factors, such as platelet-derived growth factor PDGF and hepatocyte growth factor. The Schamroth’s test is positive when the small diamond-shaped window, created by opposing the dorsal surfaces of distal phalanges of corresponding fingers of opposite hands, is obliterated.

Figure 1. Digital clubbing

photograph by Soham Vakil, MD
poem by Andrew Lerner, MD

She is a small lady, 
85 years old. 
Vitality still in her voice 
But no longer in her body. 
Unaware of the malignant vessels constricting in her arms 
And in her head. 
There is sputum on her sheet, and her scalp shows 
Through thinning hair. 
Her eyes crease genuinely when she gives me her gummy smile. 
As the years pass, she will cease to be real, 
Only a snapshot stored 
   In a neuronal circuit.

When I was 5, I took a trip 
To New York City. 
A homeless man was sitting on the sidewalk with sharp eyes. 
What is he doing right now as I write this letter? 
   Is he thinking about me?

After you leave your footprint, it 
Becomes weightless

"On Top of the World", photograph by Paurush Shah, MD
In September 2010, the ACGME Board of Directors voted to implement work rules which would among other things limit intern shifts to 16 hours effective July 2011. At Jefferson, our leadership team began working on our program's process and specific plans in attempting to rapidly adapt to the new ACGME mandates even before they were formally adopted. Together with our Chief Residents, Drs. Doug Guggenheim, Dina Halegoua, and Emily Stewart, we planned a retreat for October 22, 2010. It was held at the Union League with assembled residents from all three levels, senior administrators, and faculty that we forged our plan and response. Our goal was not only to comply, but to enhance the educational environment at Jefferson at the same time. During a preliminary Town Hall Meeting with the Interns — before we even went on retreat — we presented the new ACGME directive for informational purposes including the rationale behind the new rules. Several Interns voiced concerns about preserving education in the new work hours environment. Some asked whether the hours changes would apply to just interns or interns and residents. There was a broad discussion about the affects of a lack of sleep on errors and fatigue and the concern over car crashes post–call. As a result of this meeting we pledged to aim for 16 hour compliance for not just Interns (as the new ACGME work rules mandated), but also for Residents as well (the new rules do permit them to work 24 plus 4 hour shifts). In considering this revolutionary change, you may have several questions regarding details of our rationale. Over the past decade, a series of studies have emerged indicating that residents' traditional 24-hr work shifts pose hazards to their patients and to themselves. Elimination of 24-hour shifts has been shown in a randomized trial and other studies to reduce overall error rates. Landrigan et al, showed that houseofficers made substantially more serious errors when they worked shifts of 24 hours or more than when they worked shorter shifts (136 vs. 100 per 1000 patient days, P<0.001). While reassignment of personnel needed to support shorter work hours undoubtedly carries an up front cost (in this circumstance pulling housestaff from the BMT), a decrease in medical errors would more than pay for these costs.

Beyond patient safety, housestaff safety and education are also important. In a series of remarkable conversations I have had with many physicians who trained in the era of no hours limits, I have been amazed by the stories of near car crashes and actual car wrecks that occur driving home post call. Several well conducted studies have validated this important risk. This issue demands bold action to protect the well-being of our residents and unsuspecting motorists.

The imperative for 16 hours comes through the ACGME, I realize, but the imperative should have come from us as leaders in medical education. Whatever the case, we must answer the call and meet not only the letter of the law, but the spirit of the law as well.