To Friends of the Department of Medicine

The past year has been the most trying many of us have faced as physicians. Despite the challenges, I leave this academic year with hope and gratitude for the future of medicine. The exceptional altruism and dedication portrayed by our colleagues both within and outside the Department of Medicine made this year possible. I’ve been overwhelmed by the collegiality and dedication of all our colleagues, but specifically our residents. Despite the challenges, they have risen to every encounter with grace and poise working alongside faculty to support the Jefferson mission: We Improve Lives. In the midst of the chaos, our residents have still completed research, quality improvement projects and contributed to the humanities. This publication is just one example of the passion, dedication and creativity our residents continue to provide to the Jefferson Community. As we hope to enter a post pandemic world in the coming academic year, rest assured we have trained the strongest, most dedicated, compassionate physicians yet.

This journal, now in its 22nd edition, continues to exemplify the perseverance, inquisitiveness and talent of our Internal Medicine residents. Congratulations to the Editors and all of the residents who contributed to another amazing edition of the Forum. I hope you will enjoy reading it!

Emily Stewart, MD, FACP

Associate Professor of Medicine
Program Director Internal Medicine Residency
Dear Students, Residents, Faculty, and Friends of the Forum,

It is our honor to present the product of 22 years of resident-run tradition – the 2020-2021 annual edition of The Medicine Forum. In the world of Jefferson traditions, ours is a small one. There is no regalia, pomp and circumstance, or any such fanfare in this marking of the year’s close. Rather than the celebratory release of those other springtime occasions, this publication is a representation of the yearlong dedication and hard work of our residents and fellows in their academic pursuits.

We at The Medicine Forum know that producing scholarly work even during what would constitute a normal year can be that added stressor that just feels like too much. In a year where we have continued to see high caseloads of COVID-19 (bearing the emotional toll that comes with it to providers), scrambled to vaccinate as many of our clinic patients as possible against the disease, and tried to balance a world attempting to go back to normal during clearly abnormal times, it amazes us what you all were able to produce. To our submission writers, thank you for sharing in – despite all this – perhaps medicine’s most important practice, the furthering and dissemination of medical knowledge.

To our supporters, thank you for making this journal possible. And finally, to our readers, thank you for partaking in this, our small tradition, the 22nd edition of The Medicine Forum.

Sincerely,

Chief Editors

Xuejun Alice Wang, MD
Nivethietha Maniam, MD
Hillary Landon, MD
Jillian Cooper, MD
Joseph Grogg, MD
Akanksha Arya, MD
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“COVID Nails”

Gillian Naro, MD, MEd, Gregory Kane, MD, MACP

CASE PRESENTATION

A 73-year-old female presented to an outpatient clinic for management of her COPD. Two months prior, she had experienced a febrile illness with a cough and subsequently tested positive for the SARS-CoV-2 virus, requiring hospitalization and intubation in an intensive care unit. Physical examination revealed transverse white lines extending across the nail plate about 5mm from the base of the nail on multiple nails. These findings were consistent with Beau Lines, a sign of acute systemic inflammation resulting in the sudden interruption of nail keratin synthesis. The location of the line relative to the growth of the nail can reflect a time stamp for the moment of illness, in this case a SARS-CoV-2 infection.
Effusive-Constrictive Pericarditis due to Poorly Differentiated Carcinoma of the Mediastinum

John Wallis, MD, Naman Upadhyay, MD, Fred Karaisz MD, Mark Decaro, MD, Rene Alvarez, MD

ABSTRACT

A 33-year-old male developed subacute effusive-constrictive pericarditis with recurrent pleural effusions and mediastinal lymphadenopathy. He was found to have poorly differentiated carcinoma of the mediastinum that led to constrictive physiology not amenable to medical or surgical management, ultimately requiring hospice. This case was remarkable for its rare etiology and presentation.

LEARNING OBJECTIVES

1. Describe the novel presentation of poorly differentiated carcinoma causing effusive-constrictive pericarditis
2. Explain physiology, diagnostic findings, and management of constrictive pericarditis
3. Compare outcomes of partial vs complete pericardiectomy
4. Describe management of poorly differentiated carcinoma of the mediastinum

HISTORY OF PRESENTATION

A 33-year-old man was transferred to an academic medical center for evaluation of recurrent pleural effusions and symptoms of dyspnea and lower extremity swelling refractory to medical management and thoracentesis.

The patient initially developed idiopathic pericardial effusion with tamponade two years prior, which was refractory to anti-inflammatory medications, and was ultimately treated with a pericardial window. Pericardial biopsy at the time demonstrated chronic fibrinous pericarditis. The procedure was complicated by vocal cord paralysis requiring tracheostomy. He underwent an autoimmune work up which was unremarkable, and no underlying etiology was identified.

After the pericardial window, the patient was asymptomatic and able to return to employment at a supermarket. After two years, the patient developed recurrent volume overload. Over the subsequent 9 months, he required frequent hospitalizations for intravenous diuresis. Transthoracic echocardiogram at the outside facility reportedly showed a complex circumferential pericardial effusion. He was transferred to our facility when his symptoms did not improve despite diuresis and thoracentesis.

On admission he was tachycardic to 108 beats/min with blood pressure 106/86 mm Hg. Heart auscultation revealed distant heart sounds with no murmur or pericardial friction rub. Jugular venous pressure was difficult to assess due to obesity. Skin was warm. His abdomen was distended, and his legs were markedly swollen. Laboratory results were as follows: electrolytes were remarkable for sodium of 122 mmol/l and bicarbonate concentration of 37 mmol/l, liver enzymes were remarkable for total bilirubin of 2.2 mg/dL and alkaline phosphatase of 261 IU/L. Whole blood lactate was 2.4 mmol/l.

An electrocardiogram revealed sinus tachycardia with premature ventricular contractions, biatrial enlargement, and non-specific repolarization changes. A chest radiograph showed enlargement of the cardiac silhouette, mild pulmonary edema and a layering right pleural effusion. Echocardiography revealed calcified thickened echogenic material in the pericardial space and showed annulus reversus with early diastolic septal bounce and small LV cavity size - concerning for constrictive pericarditis (Figure 1).
PAST MEDICAL HISTORY

The patient had a history of effusive constrictive pericarditis status-post pericardial window with recurrent bilateral pleural effusions and ascites with unclear etiology.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included constrictive pericarditis (CP) related to malignancy, rheumatologic causes (scleroderma), or alternative causes (viral, idiopathic), chronic diastolic heart failure, or cardiac tamponade.

INVESTIGATIONS AND MANAGEMENT

Cardiac MRI showed a complex circumferential pericardial effusion in which the parietal and visceral layers of the pericardium were not distinctly identified from the complex fibrinous pericardial process. There was significant enhancement of the pericardial fluid on late gadolinium enhanced images, with small focal areas of calcifications in the pericardial space.

Due to concern for malignancy, the patient underwent a CT scan of his chest which demonstrated extensive mediastinal adenopathy with lymphangitic spread into the right lung, suggestive of lymphoma. The CT noted high density material within the expected pericardial space with irregularity of the epicardial fat, suggestive of soft tissue involvement. PET-CT showed intense activity corresponding to the complex pericardial fluid, mildly avid diffuse mediastinal lymph nodes, and heterogeneous increased background level activity throughout. His pleural fluid was exudative, culture-negative, lymphocytic-predominant, with negative cytology on multiple samples. Repeat autoimmune workup for serositis was negative.

Right heart catheterization showed elevated and equilibrated right and left ventricular end-diastolic pressure (24 to 28 mm Hg). At the time of catheterization, the mean pulmonary artery pressure was 35 mm Hg, with pulmonary vascular resistance of 3.14 WU. A dip-and-plateau pattern was noted, with rapid x and y descents on right atrial pressure with ventricular interdependence. Fick cardiac index was noted to be 1.36 L/min/m2.

The patient was started on high dose diuretics. A trial of low dose dobutamine did not provide clinical benefit. He had already failed to benefit from anti-inflammatory medications previously. There was no free fluid to remove by pericardiocentesis. As he was not responding to medical management, the patient was taken by cardiothoracic surgery for mediastinal exploration with a plan for pericardiectomy. Upon access to the mediastinal space, diffuse lymphadenopathy with necrotic lymph nodes were noted. The pericardium was diffusely thickened and densely adherent to the epicardium, which prohibited pericardiectomy. Biopsies of the pericardium and surrounding lymph nodes were taken along with sampling of the pericardial fluid.

The patient was briefly initiated on steroids for possible lymphoma per oncology, which were discontinued when his pericardial fluid flow cytometry was negative. The final pathology report of his pericardium and surrounding lymph nodes was significant for high grade poorly differentiated carcinoma of the mediastinum (figures 2 and 3).

Figure 2: Hematoxylin and eosin stain of pericardial biopsy showing poorly differentiated carcinoma (10x magnification).

Figure 3: Hematoxylin and eosin stain of mediastinal lymph node showing poorly differentiated carcinoma (5x magnification).
OUTCOMES & FOLLOW-UP

The patient continued to deteriorate from cardiogenic shock. He required mechanical ventilation via his tracheostomy, but his respiratory status continued to worsen. He developed sepsis due to ventilator-associated pneumonia. Given his rapid deterioration in the setting of an aggressive malignancy with limited treatment options, oncology determined he would be unlikely to benefit from anti-cancer directed therapy. Ultimately, the patient and family decided to transition to comfort-based care at an inpatient hospice facility.

DISCUSSION

This report highlights a case of poorly-differentiated carcinoma of the mediastinum causing constrictive pericarditis, a pathophysiologic entity that has not been previously described based on our literature review. We will discuss the background and management of effusive-constrictive pericarditis, the association with malignancy, and the management of poorly differentiated carcinoma of the mediastinum.

Effusive-Constrictive Pericarditis

Chronic inflammation of the pericardium can lead to thickening, fibrosis, and calcification of the pericardium. This leads to inelasticity, which prevents diastolic filling of the ventricles. Patients develop low stroke volume, which decreases their cardiac output. Patients typically present with signs of right-sided heart failure, such as jugular venous distension, edema/anasarca, ascites, and pleural effusions. Idiopathic, viral, and post-procedural (cardiac surgery, radiation therapy) are the most common causes in the developed world, while infectious (tuberculosis) etiologies are the most common in developing countries. Patients with more severe cases of pericarditis (fever, large effusion, tamponade, failure to respond to NSAIDs) are more likely to develop constrictive pericarditis.

Management of Constrictive Pericarditis

Constrictive pericarditis is often initially treated with anti-inflammatory medications such as colchicine and NSAID’s. Cardiac MRI can be used to assess for active inflammation to guide treatment. Some patients will have improved pericardial compliance with resolution of inflammation. Specific therapies can be tailored to the underlying etiology - e.g., tuberculous pericarditis should be treated with anti-tuberculous therapy. Diuretics can be used for symptom relief. However, patients will often have elevated filling pressures even if euvoletic. Pericardiocentesis can be performed if pericardial effusion or tamponade are present.

If anti-inflammatory treatments are not successful, the inelasticity of the pericardium is likely irreversible, and the next step would be to surgically strip the pericardium (pericardiectomy). Pericardiectomy historically carried high surgical risk, with a reported hospital mortality ranging from 4.9% to 12%. However, survival without surgery is poor, and surgery can improve symptoms and functional status in the majority of patients. Patients with low left ventricular ejection fraction, right ventricular dilation, atrial fibrillation, poor functional class, hepatomegaly or hepatic dysfunction, diabetes, coronary artery disease, COPD, renal dysfunction, or effusive-constrictive pericarditis prior to surgery have poorer outcomes. Earlier surgery may improve outcomes, specifically if performed within 6 months of symptom onset. Among patients who survived to discharge, survival at five years after surgery ranges from 78-94.6%. One study of 97 patients undergoing surgery for constrictive pericarditis had a 30-day survival rate of 81.4%, 1-year survival of 66.5%, and 5-year survival of 51.6%, with no difference based on underlying etiology.

Surgical approach is still controversial. There are more conservative approaches, such as an anterior pericardiectomy that only removes the anterior pericardium between both phrenic nerves. A more aggressive complete pericardiectomy removes the anterior, inferior (diaphragmatic), and left lateral pericardium. Cardiopulmonary bypass may or may not be necessary. There are mixed results regarding risk and benefits of either approach. In one study of 130 anterior pericardiectomies, 91% initially had NYHA functional class III or IV, whereas at 1 year after surgery, 88% of patients were NYHA functional class I or II. This indicates that anterior pericardiectomy may be sufficient. However, another study of 37 anterior pericardiectomies and 53 complete pericardiectomies actually showed better survival rate, functional status, right ventricular systolic pressure, and less tricuspid regurgitation in patients with complete pericardiectomy. One study of 395 patients showed that patients undergoing partial periadicectomy had worse outcomes including higher operative mortality, more post-operative low-output syndrome, longer hospitalization, worse long-term survival, slower functional recovery, and increase risk of recurrent symptoms compared to complete pericardiectomy.

Patients may have an outer rind that is easily removed, but a second epicardial covering causes continued constriction. If it is not possible to remove the pericardium completely, then the peel may be incised to create non-contiguous constriction.

Interestingly, tricuspid regurgitation (TR) often accompanies CP, and moderate to severe TR is associated with worse survival in patients with CP. While still controversial, some experts recommend concomitant tricuspid valve repair at the time of pericardiectomy to improve long-term survival.
Management of poorly differentiated carcinoma of the mediastinum

Poorly differentiated carcinoma of the mediastinum is a rare tumor in which the primary site of origin is unable to be identified based on histopathological features. This rare type of tumor has low survival. Further investigation can often identify the underlying diagnosis, which may have specific therapeutic options. If levels of α-fetoprotein or HCG are elevated, then patients should be treated for mediastinal nonseminomatous germ cell tumor. If bronchoscopy shows an endobronchial lesion, then the patient should be diagnosed with lung cancer. If there are neuroendocrine features, then the patient should be treated for small-cell lung cancer. Without any other clear evidence, the patient should be treated for non-small cell lung cancer. Poorly differentiated carcinoma with neuroendocrine features among patients without lung cancer risk factors should be treated with platinum/etoposide with or without paclitaxel. Surgical resection and local radiation can treat tumors confined to the mediastinum, usually along with chemotherapy. One study treated 43 patients with poorly differentiated carcinoma or adenocarcinoma with cisplatin-based chemotherapy. 13 patients (30%) had complete response, and 7 patients (16%) are long-term disease-free survivors. Therefore, patients should be treated based on the specific tumor type that is identified with further analysis, and platinum/etoposide-based chemotherapy should be used in patients whose specific tumor could not be identified.

If constriction and malignancy were detected in our patient at an earlier stage in the disease process, he may have benefited from early pericardial stripping. This may have provided more time with improved functional status, during which he may have been stable enough to receive treatment for the underlying malignancy with platinum/etoposide. Unfortunately, by the time he arrived at our institution, he could not undergo pericardial stripping because the tumor had invaded into the myocardium, and he was too unstable to undergo treatment for his malignancy.

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Acute Mitral Regurgitation Presenting with Right Upper Lobe Opacification

John Wallis, MD and Mark Decaro, MD

Key Words: Acute mitral regurgitation, Papillary muscle rupture, Unilateral pulmonary edema

ABSTRACT

We describe a rare entity in which acute mitral regurgitation causes asymmetric findings on chest radiograph. The patient presented with rapid-onset respiratory failure from flash pulmonary edema. She had unilateral infiltrates on chest radiograph, which evoked infectious etiology. However, we identified a flail mitral valve leaflet, for which the patient received an emergent mitral valve replacement. Fortunately, she made a full recovery. We discuss the mechanism of the asymmetric chest radiograph findings, which we were able to confirm using a transesophageal echocardiogram.

CASE PRESENTATION

A 62-year-old female presented to the emergency department in acute respiratory failure. Her past medical history included obesity, asthma, hypertension, diastolic heart failure, and mild-moderate mitral regurgitation. She arrived unresponsive via EMS with an oxygen saturation of 23% for which she was immediately intubated. She required maximal ventilator settings (FiO2 100%, PEEP 16) and neuromuscular blockade to achieve adequate oxygenation.

Initial chest radiograph demonstrated diffuse opacities with dense consolidation in the right upper lobe (Figure 1). Subsequent chest radiographs showed near-complete opacification of the right hemithorax (Figure 2).

These asymmetric lung findings were suspicious for infectious etiology, including Covid-19 or bacterial pneumonia causing ARDS. The patient’s family informed us that she had felt normal upon awakening, and developed sudden shortness of breath when ambulating to the bathroom. This history of rapid progression is less consistent with infectious causes. She was afebrile and had no respiratory secretions. She tested negative for Covid-19, including from a tracheal aspirate. She had a mild leukocytosis of 12.4 with only 52% neutrophils, normal procalcitonin (0.05 ng/mL), and an unimpressive C-reactive protein (0.90 mg/dL). These results were inconsistent with severe infection, so we investigated cardiac etiologies.

Initial ECG showed sinus tachycardia at 132 bpm with no ischemic changes. High-sensitivity troponin was 66 ng/L initially, increased to 144 ng/L, and then peaked at 151 ng/L before downtrending. She was treated for acute coronary syndrome with aspirin, statin, and an unfractionated heparin drip, although her troponin elevation was most likely a result of profound hypoxia. Her pro-BNP
was 246 pg/mL. A transthoracic echocardiogram showed normal biventricular function, but detected a flail anterior mitral valve leaflet with significant mitral regurgitation with an eccentric jet. The patient was growing more hypotensive requiring vasopressors, her extremities were becoming cool, and she was anuric despite diuretics, consistent with cardiogenic shock. Her respiratory status had somewhat stabilized.

The patient was emergently transferred to our main campus where she had an intra-aortic balloon pump placed for afterload reduction. A transesophageal echocardiogram confirmed severe mitral regurgitation and showed a ruptured anterior papillary muscle (Figure 3). This TEE showed severe systolic flow reversal in the right upper pulmonary vein, with only mild systolic flow reversal in the three other pulmonary veins. She underwent coronary angiography showing no obstructive coronary artery disease. She was taken to the OR for an emergent bioprosthetic mitral valve replacement. Afterwards, her clinical status improved, she began making urine, her pulmonary artery pressures corrected, and she was extubated 72 hours after presentation. Subsequent chest x-rays showed rapid resolution of the asymmetric infiltrates (Figure 4).

**DISCUSSION**

This was a dramatic presentation of spontaneous, non-ischemic papillary muscle rupture causing severe acute mitral regurgitation, with respiratory failure from resultant flash pulmonary edema. She was critically ill within minutes of symptom onset. The patient is fortunate to have a positive outcome. Of particular interest is the initial chest radiograph showing asymmetric opacification with dense consolidation of the right upper lobe. This appearance sent us down an infectious diagnostic pathway, which could have delayed the diagnosis.

There is previous literature describing this phenomenon. Focal or unilateral pulmonary edema has been described in patients with mitral regurgitation from numerous causes, including spontaneous valve perforation\(^1\), valve perforation due to infectious endocarditis\(^2\), transient papillary muscle dysfunction due to myocardial ischemia\(^3\), or spontaneous papillary muscle or chordae tendineae rupture.\(^4\)\(^\text{-}\)\(^6\) Case reports show that this finding is often initially mistaken for pneumonia or other respiratory illnesses.\(^7\)

Schnyder et. al found that 9% of patients with severe mitral regurgitation had chest radiograph findings that were “localized or predominant” in the right upper lobe.\(^8\) Attias et. al studied 869 patients admitted with cardiogenic pulmonary edema, and found that 2.1% had unilateral pulmonary edema (UPE). Notably, all of the patients with UPE were found to have severe mitral regurgitation. Of patients with cardiogenic pulmonary edema and severe MR, 75% had bilateral findings and 25% had unilateral findings.
Only 6% of patients with bilateral pulmonary edema received antibiotics, whereas 61% of patients with unilateral pulmonary edema received antibiotics. This shows that focal chest radiograph findings often invoke infectious etiology among clinicians.

Outcomes are widely divergent depending on initial imaging findings. Patients with UPE were found to have significantly lower blood pressure on presentation, higher use of NIPPV/IPPV, and more frequent use of vasopressors/inotropes. Patients with severe MR had an in-hospital mortality of 39% when presenting with unilateral findings, compared to 6% when presenting with bilateral findings. Therefore, presentation with focal radiographic findings not only delays the diagnosis, but has been shown to correlate with worse outcomes and death.9

There is a proposed mechanism for localized pulmonary edema due to MR. Typically, systolic or diastolic left ventricular failure leads to increased pressure within the left atrium, which is transmitted symmetrically to each of the pulmonary veins. This leads to increased hydrostatic pressure within pulmonary capillaries, causing a uniform degree of pulmonary edema throughout the lungs.

It is thought that asymmetric pulmonary edema is due to a mitral regurgitant jet that propels blood selectively towards the orifice of a particular pulmonary vein within the left atrium. If a regurgitant jet causes increased pressure within that pulmonary vein, it would transmit increased hydrostatic pressure selectively to the pulmonary capillaries that drain into that pulmonary vein, causing focal edema.

This mechanism is supported by Kashiura et al., who described two cases of unilateral pulmonary edema from severe acute MR. The first case had an eccentric jet blowing towards the right side of the left atrium and presented with right-sided opacities. The second case had a jet blowing towards the left side of the left atrium, and that patient presented with left-sided opacities.2 This indicates that the direction of the regurgitant jet affects which pulmonary veins are selectively pressurized, which correlates with focal edema. In our case, the regurgitant jet was directed towards the right upper pulmonary vein, which drains the right upper and middle lobes, causing right upper lung opacification. The patient’s TEE confirmed severe systolic flow reversal within the right upper pulmonary vein, which provides evidence supporting this mechanism.

As in our case, acute mitral regurgitation can present with sudden life-threatening respiratory failure and cardiogenic shock, so prompt diagnosis is critical. It is often misdiagnosed as pneumonia or other respiratory illness. Patients with this finding have worse outcomes and delays in diagnosis and treatment compared to similar patients with bilateral pulmonary edema.9 In our case, the key to the diagnosis was the reported history of sudden-onset dyspnea that progressed to respiratory failure within minutes.

In conclusion, acute mitral regurgitation should be considered in the differential diagnosis for patients with focal right upper lobe opacities in the appropriate clinical context — such as sudden-onset hypoxic respiratory failure, especially if vitals, exam, and laboratory biomarkers are inconsistent with severe infection. Awareness of this entity could be life-saving. Our findings support the previously proposed mechanism of a regurgitant jet selectively pressurizing the right upper pulmonary vein, leading to right upper lobe edema.

REFERENCES

Severely Impaired Gastric Emptying in the Setting of an Extensive Malignancy History: A Case of Paraneoplastic Gastroparesis

Gregory Habig MD, Justin Robbins MD

INTRODUCTION

Gastroparesis is a disorder of the stomach involving a delay in the emptying of gastric contents that typically presents with nausea, vomiting, early satiety, and weight loss. Though commonly associated with diabetes or as a complication of surgical procedures, etiologies stemming from paraneoplastic processes are important to consider despite often being overlooked. The case presented here describes a patient with a significant malignancy history and evidence of severely impaired gastric emptying concerning for paraneoplastic gastroparesis and highlights the evaluation, diagnosis, and management of the condition.

CASE PRESENTATION

The patient is a 73-year-old man with a past medical history notable for chronic lymphocytic leukemia recently on ibrutinib, prostate cancer s/p surgical resection, non-small cell lung cancer s/p pulmonary lobectomy, hypothyroidism, and hepatitis C cirrhosis who presented to the office for evaluation of poor oral intake, inability to carry out activities of daily living, and altered mental status. History was limited given the patient’s poor mental status, however he did endorse 15lb weight loss and decreased appetite. He denied any nausea, vomiting, abdominal pain, or change in bowel habits. Physical exam was notable for an overall frail appearance with dry mucous membranes, and an abdominal exam without distention, or tenderness to palpation. Cardio-pulmonary examinations were unremarkable. Relevant laboratory data included a TSH of 0.48 uU/L (0.30-5.00 uU/mL), and a hemoglobin A1c 4.9 (NL<5.7%) obtained 5 months prior. The patient recently received a gastric emptying study which showed severely impaired gastric emptying with 50% gastric retention at greater than 28.5 hours (NL <10% retained at four hours). Computer Tomography (CT) showed evidence of diffuse lymphadenopathy, a new hepatic hypodensity, but no evidence of extrinsic compression of the gastric outlet. Anti-Jo1 Ab and Hu antibodies were sent to further evaluate for a possible paraneoplastic etiology however he was discharged home prior to these tests resulting given his clinical stability.

DISCUSSION

Paraneoplastic Gastroparesis, although an uncommon cause of delayed gastric emptying, is an important diagnosis to consider in severe cases without other obvious etiologies. Although diabetes and surgical complications account for greater than 42 percent of cases of gastroparesis, paraneoplastic syndromes should not be excluded as a possible cause of delayed gastric emptying as it can often be the presenting symptom of an underlying malignancy. Paraneoplastic gastroparesis has most commonly been observed in patients with lung, pancreatic, gallbladder, uterine or other soft tissue malignancies. Knowing these common associations is an important factor to consider when evaluating a patient with delayed gastric emptying and concurrent cancer as it can inform one’s clinical suspicion for a paraneoplastic cause. Even when comorbidities that are more commonly associated with gastroparesis are present, malignancy should always be considered.

In patients with a significant history of malignancy as presented here, identifying and resolving confirmed cases of paraneoplastic gastroparesis relies on successful identification of the underlying malignancy through tissue diagnosis via biopsy. A less invasive method for screening for paraneoplastic gastroparesis prior to attempting biopsy is through serologic testing. A case series by Lee et al. focused on the evaluation of paraneoplastic gastrointestinal motility dysfunction and noted positive paraneoplastic antibodies in 10 of 11 cases reviewed. Despite small study populations, similar studies support antibody screening with type 1 antineuronal nuclear antibody (ANNA-1 or anti-Hu antibody) and cytoplasmic purkinje cell (Anti-Yo) antibodies in patients with suspicion for paraneoplastic gastroparesis. Serology testing has become an important step in the diagnosis of paraneoplastic gastroparesis. The paraneoplastic syndrome is confirmed with the detection of positive onco-neural antibodies or onset of symptoms within five years of the development of cancer. Baig et al. highlighted that diagnosis likely holds prognostic value as well given that patients with paraneoplastic gastroparesis showed symptomatic improvement after surgical resection, chemotherapy, or radiation treatment of underlying malignancy in 6 of 14 cases reviewed. Traditional therapies for gastroparesis
such as frequent small meals, anti-emetics, and pro-kinetic agents like metaclopromide and erythromycin are still utilized to help alleviate symptoms.

The case presented here demonstrates the need to fully investigate symptoms of weight loss, poor oral intake, nausea, and vomiting in this patient population as they could be explained by and lead to the diagnosis of a new disease process such as paraneoplastic gastroparesis. This case highlights severely pathologic gastric emptying in a patient with a significant history of malignancy and emphasizes the importance of considering a paraneoplastic syndrome as a possible cause of gastroparesis. Delayed gastric emptying, especially in patients with underlying malignancy is an often overlooked disease process that requires thorough evaluation with imaging and serologic testing.

REFERENCES


A Case of Native Hip Pseudomonas aeruginosa Septic Arthritis Caused by Vesico-acetabular Fistula

Tudor Sturzoiu

ABSTRACT

A 61-year-old man with a past medical history significant for metastatic rectal cancer treated with local resection, chemotherapy, and radiation complicated by vesicocutaneous fistula presented with subacute ambulatory dysfunction secondary to right hip pain. Imaging studies were consistent with a right hip effusion, and fluoroscopy-guided hip aspiration revealed septic arthritis caused by Pseudomonas aeruginosa. Resistance patterns identified this strain of Pseudomonas to be the same one that caused pyelonephritis that was treated during the same hospitalization. Although further diagnostic imaging was not pursued, the presentation was most consistent with vesico-acetabular fistula causing native hip septic arthritis. This is a very rare complication of radiation therapy that serves as a reminder to keep a broad differential for atypical presentations in patients who have undergone extensive local radiation.

INTRODUCTION

Pelvic radiation therapy is commonly part of a multimodal therapeutic approach for malignancies involving abdominopelvic organs. While it can be effective, it has also been associated with many complications stemming from damage to surrounding structures, including radiation-induced colitis/proctitis, ureteral strictures, and various types of fistulae.

While many types of fistulae have been characterized and reported, vesico-acetabular fistulae are relatively rare. Here, we present a case of a 61-year-old man who had undergone treatment for rectal cancer with pelvic radiation approximately 1 year prior to presenting with native hip septic arthritis caused by a vesico-acetabular fistula.

CASE REPORT

Our patient had metastatic rectal cancer that was treated with rectal tumor resection, chemotherapy, and pelvic radiation 5 years prior to presentation. Due to local recurrence, he was once again treated with chemotherapy and pelvic radiation (3,600 centi-gray over 30 fractions) one year prior to presentation. Over the following year, he developed a large vesico-cutaneous fistula that resulted in persistent drainage of urine from his perineum. Treatment for this complication was attempted with implantation of bilateral percutaneous nephrostomy tubes intended to divert urine from the bladder, but perineal drainage of urine persisted. One year after undergoing radiation, he presented to the hospital with acute on chronic kidney disease, fever, pyelonephritis, and ambulatory dysfunction secondary to right hip pain. He was also experiencing increased drainage of urine from his perineum, and he reported that his urine had become foul-smelling. Recent outpatient magnetic resonance imaging of the right hip, which was obtained following a fall, demonstrated stable osteoarthritis with a new right hip effusion and right iliopsoas bursitis.

Vital signs on presentation included temperature 101.5 F, heart rate 86 beats per minute, respiratory rate 16 breaths per minute, blood pressure 109/60 mmHg, and oxygen saturation 99% on room air. Physical exam was significant for cachexia and a clean perineal wound that was notably draining foul-smelling urine with no associated surrounding soft tissue changes. Right hip examination was significant for tenderness to palpation along the greater trochanter as well as pain with micromotion. Full range of motion could not be tested secondary to significant pain and guarding. Initial labs were significant for creatinine 3.4 mg/dL (baseline 2.0 mg/dL), white blood cell count 7.5 B/L with a normal differential, and hemoglobin 6.4 g/dL (baseline 8.0 g/dL) - the rest of his basic metabolic panel and complete blood count were unremarkable. Urinalysis showed 2+ blood, 3+ leukocyte esterase, negative nitrites, and >182 WBC per high powered field. Urine cultured from bilateral percutaneous nephrostomy tubes prior to exchange grew Pseudomonas aeruginosa susceptible to most antibiotics. Blood cultures drawn on the same day remained negative for 5 days.

He was treated for pyelonephritis with cefepime and his bilateral percutaneous nephrostomy tubes were exchanged. Due to his progressive ambulatory dysfunction, continued fevers, and recent right hip MRI demonstrating a right hip joint effusion, there was high concern for septic arthritis of the right hip. At this time, C-reactive protein and erythrocyte sedimentation rate were 18.3 mg/dL and 91 mm/hr respectively. He underwent fluoroscopy-guided aspiration of the right hip, which revealed cloudy fluid with a white blood cell count of 30,974 per ul (95% neutrophils) and a glucose
of 26 mg/dL; cultures of this fluid grew Pseudomonas aeruginosa with the same antimicrobial resistance pattern as that in his urine. While no diagnostic studies were undertaken to directly assess the presence of a fistulous tract between the bladder and the hip, this was thought to be the most plausible explanation for his pathology given his history. Orthopedic surgery was consulted, and he underwent right hip arthrotomy with debridement and washout. During the procedure, they encountered and debrided an abscess in the rectus femoris as well as copious purulent fluid within the right hip capsule. A fistulous tract was not directly visualized at the time of surgery. The patient did not experience any immediate complications from the surgery. While the patient’s pain did improve significantly following this intervention, he did not regain significant ambulatory function secondary to failure to thrive, and he unfortunately passed away on hospice shortly after discharge from the hospital.

DISCUSSION

This case highlights the unique anatomical complications that can occur in patients with soft tissue tumor invasion, especially following extensive local radiation. Our patient presented with subacute hip pain caused by septic arthritis secondary to likely vesico-acetabular fistula. No diagnostic study directly visualized the fistulous tract, but it is the most plausible explanation given the patient’s history. Osteomyelitis with ensuing septic arthritis can occur due to hematogenous seeding, but this patient’s blood cultures were never positive, and he had known fistulous connections between his bladder and other pelvic structures as a result of radiation. It is interesting to note that this patient’s septic arthritis presented with no signs of systemic inflammation aside from persistent fevers, elevated ESR, and elevated CRP, all of which can be difficult to interpret in the setting of advanced metastatic disease.

Fistulae between the bladder and various surrounding structures in the setting of pelvic radiation are not uncommon and have been reported on extensively in the literature. It is also known that fistulae are more likely to occur as complications of surgery in the setting of prior pelvic radiation, but our patient did not have any prior surgical procedures that could predispose him to pelvic fistulization.

While there are a number of cases of vesico-acetabular fistulas reported in the literature, all that we reviewed were in the setting of primary hip pathology and as a complication of hip surgery. These generally occur within a few months to years after radiation. In our case, it was 1 year after radiation, but it has been reported as far out as 35 years following radiation. We did not find any other cases of vesico-acetabular fistulae associated with pelvic radiation.

CONCLUSION

We believe our case to be a unique example of the type of complication that can occur in the setting of locally invasive malignancy managed with radiation. The most important takeaway from this case is that the anatomy of an irradiated area can become significantly altered, and pathology arising from this should be carefully considered when dealing with problems involving these areas. Significant morbidity can arise from these changes in anatomy, and earlier identification and treatment can enable more expedient treatment and prevent further complications.

REFERENCES

Carbamazepine Induced Bullous Pemphigoid in a 49 Year Old Male

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ABSTRACT

Bullous pemphigoid is an autoimmune blistering condition mediated by autoantibodies. It is categorized as an uncommon disorder, with an estimated incidence of 2.4-21.7 cases per million but carries significant morbidity and mortality, warranting clinical awareness and investigation. A number of medications have been implicated in the development of bullous pemphigoid including loop diuretics, ace inhibitors, and anti-epileptic drugs.

This is a case report of carbamazepine-induced bullous pemphigoid in a 49-year-old male after taking the medication for almost 30 years. Diagnosis of bullous pemphigoid was based on biopsy histology and immunofluorescence, as well as the presence of BP 180 antibody. Clinical features of extensive rash and bullae were present on dermatological exam. Upon discontinuation of carbamazepine and appropriate treatment of bullous pemphigoid, the patient’s condition improved. A thorough analysis of the patient’s history and medications did not reveal any other potential triggers of bullous pemphigoid.

The only two previous reports of an association between carbamazepine and bullous pemphigoid are limited by lack of immunologic evidence of diagnosis or the identification of a specific causative agent. To address these limitations, we describe what is to our knowledge, the first reported case of clearly documented association between carbamazepine and bullous pemphigoid.

BACKGROUND

Bullous pemphigoid is an autoimmune blistering condition mediated by autoantibodies. It is categorized as an uncommon disorder, with an estimated incidence of 2.4-21.7 cases per million. Bullous pemphigoid carries significant morbidity and mortality. Mortality rates in the US range from 11-23%. Risks associated with this condition include dehydration, superimposed infection, and scarring. Bullous pemphigoid may develop spontaneously or be triggered by infection or medication. A number of medications have been implicated in the development of bullous pemphigoid including loop diuretics, ace inhibitors, and anti-epileptic drugs. There are 2 case reports available which claim an association between BP and carbamazepine.

CASE

A 49-year-old male, with a past medical history significant for cerebral palsy and seizure disorder well-controlled on carbamazepine, presented with worsening bullous pemphigoid diagnosed at an outside hospital. He was admitted due to worsening of his condition despite topical and oral corticosteroid treatment. The rash presented as blistering on his trunk and all four extremities. There was no mucosal involvement. The patient and his family denied any new medications, foods, illnesses, or environmental exposures. Dermatological exam noted tense bullae filled with clear to straw-colored fluid primarily on the trunk and thighs but also on the more distal extremities. Ruptured bullae with overlying crust were also present, especially on the hands and feet. Nikolsky sign was negative.

The diagnosis of bullous pemphigoid was confirmed with the presence of linear basement membrane deposits on immunofluorescence. Direct immunofluorescence analysis of a skin biopsy demonstrated intralesional IgG deposition and linear immunofluorescence at the dermal-epidermal junction of lesions. Additionally, BP 180 antibody testing was positive with a serum concentration of 126 U/mL.

The patient’s home medication list, which included aspirin, lorazepam, trazodone, and carbamazepine, was reviewed to identify potential causes of bullous pemphigoid other than carbamazepine. Other than carbamazepine, none of these medications are associated with serious skin conditions or bullous pemphigoid. Therefore, carbamazepine was discontinued and switched to levetiracetam for seizure prophylaxis. After the removal of carbamazepine and initiation of rituximab for treatment-refractory bullous pemphigoid, no new lesions developed. Six weeks after discharge the patient’s condition continued to improve.
Figure 1: Physical exam findings of widespread bullous skin eruption. Multiple tense bullae present on trunk and ruptured bullae present on distal extremities.

**DISCUSSION**

Carbamazepine is an anticonvulsant that is associated with serious, even fatal dermatologic reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Autoimmune blistering conditions such as bullous pemphigoid are not among the known skin reactions caused by carbamazepine. There are only two reports of an association between carbamazepine and bullous pemphigoid. The first describes the development of bullous pemphigoid after carbamazepine overdose. However, direct immunofluorescence was not conducted and serum studies were reported to be negative. The second report describes the development of bullous pemphigoid in a patient taking carbamazepine, zonisamide and minocycline. Lesional biopsy plus direct and indirect immunofluorescence indicated bullous pemphigoid as the diagnosis. However, clinical
improvement was noted after the removal of all three medications and reintroduction was not attempted with any of the implicated medications. Moreover, results of drug-induced lymphocyte stimulation tests for carbamazepine, zonisamide and minocycline hydrochloride were negative.

This study has overcome the limitations of previous reports. Bullous pemphigoid was confirmed clinically with improvement after the removal of carbamazepine, immunohistologically with biopsy and direct immunofluorescence, and serologically with the identification of BP 180 antibodies. The probable relationship between the adverse effect of bullous pemphigoid and carbamazepine was also indicated with use of the Naranjo Adverse Drug Reaction Probability Scale, which is consistent with our conclusion that carbamazepine was the likely cause of bullous pemphigoid. The primary limitation of this study is that reintroduction of carbamazepine was not attempted.

Thus, we present this as the first report of proven bullous pemphigoid in association with carbamazepine use. The goal of this report is to create awareness of this association in order to encourage clinical vigilance and the reporting of similar findings in the future.

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New-Onset Rheumatologic Disease in an Elderly Patient Initially Presenting as Worsening Sequelae of Longstanding Peripheral Vascular Disease

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that is believed to activate and attack nuclear antigens in genetically susceptible individuals after exposure to environmental factors causing cell damage.1,2 Although it is most common in females of child-bearing age, initial presentation is not strictly limited to this population, as onset over the age of 50 years is reported in 3-18% of cases.2 The common manifestations of SLE affect nearly every system of the body and may include arthralgia, myalgia, fever, rash, hepatosplenomegaly, lymphadenopathy, pleuritis, glomerulonephritis, pericarditis and neuropsychiatric manifestations.1-3 Common laboratory findings in SLE with varying degrees of sensitivity and specificity include anti-nuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA), anti-histone antibodies, elevated inflammatory markers, and decreased levels of complements C3 and C4.1 Treatment is typically aimed toward symptom management and prevention of organ damage; thus, treatment regimens are typically dictated by the organ systems involved and symptoms experienced.1

Hydralazine, a vasodilating drug used for treatment of hypertension, has been demonstrated to cause various rheumatologic complications, including a lupus-like syndrome and an anti-neutrophil cytoplasmic antibody (ANCA) vasculitis, which tend to present with overlapping features.3-5 Notably, both of these hydralazine-induced rheumatologic diseases tend to present similarly to their primary counterparts but with less severity and less organ involvement; however, hydralazine-induced lupus is particularly prevalent in the elderly population whereas the limited data available regarding hydralazine-induced ANCA vasculitis is inconclusive regarding a predominant age-group affected.3-5 The definitive treatment of both of these complications of hydralazine therapy is early identification and intervention with cessation of hydralazine therapy, given that in both diseases, symptoms typically resolve upon cessation of the offending agent.3,4 With this treatment in mind, cessation of the offending agent can also be diagnostic in terms of determining whether a patient’s clinical presentation is due to primary or drug-induced rheumatologic disease. Here, we present a 78-year-old woman, Mrs. J, who was on long-term hydralazine therapy with apparently worsening complications of her known peripheral artery disease, chronic kidney disease, and type 2 diabetes mellitus and was subsequently found to have several findings concerning for new-onset underlying rheumatologic disease, possibly hydralazine-induced.

CASE PRESENTATION

Mrs. J is a 78-year-old woman who presented to Thomas Jefferson University Hospital (TJUH) from an outpatient rehabilitation facility for transient altered mental status. She has a medical history of coronary artery disease with right coronary artery stent, type 2 diabetes mellitus (T2DM), hypertension previously controlled with hydralazine until December 2020, type 2 diabetes mellitus (T2DM), hypertension previously controlled with hydralazine until December 2020, chronic kidney disease, permanent pacemaker secondary to complete heart block, interstitial lung disease (ILD) diagnosed in January 2020 and complicated by severe pulmonary hypertension leading to cor pulmonale, and stage 1A invasive ductal carcinoma of the breast previously treated with Anastrazole and partial mastectomy in August of 2020. She had been discharged for one day after being admitted to TJUH for 19 days for weakness and generalized pain. During that admission, she was also found to have an acute kidney injury (AKI), which was concerning for underlying rheumatologic etiology. Workup at that time demonstrated elevated PL-12 antibody, which is commonly associated with myositis, but her presentation was not consistent with dermatomyositis or polymyositis. Rheumatologic studies also showed elevated anti-nuclear antibody (ANA) with titer of 1:320 and homogenous pattern, positive anti-myeloperoxidase (MPO) and anti-proteinase 3 (PR3) antibodies with titer of 1:640, and anti-double stranded DNA (dsDNA) antibody elevated to 889 IU/mL (normal = < 200 IU/mL). Nephrology concluded that her AKI was most likely due to nonsteroidal anti-inflammatory drug (NSAID) use, poor oral intake, and secondary autoregulatory failure due to angiotensin receptor blocker (ARB) use at home. She also had a sacral decubitus ulcer determined by dermatology to be most likely due to...
reactivation of latent herpes simplex virus (HSV) infection and exacerbated by decreased mobility and failure to thrive, so she was prescribed a one-week course of valacyclovir. Lastly, she had painful discoloration of her bilateral toes, most likely due to cholesterol emboli. Vascular surgery obtained an ankle brachial index (ABI) pulse volume recording (PVR) study due to concern for ischemia, which showed right ABI of 0.50 and left ABI of 0.53, indicating severe and mild to moderate peripheral vascular disease respectively. They recommended continuing dual antiplatelet therapy and high-intensity statin and following up with them as an outpatient.

During the present admission, her previously identified medical problems persisted with her acute kidney injury worsening as indicated by persistent microscopic hematuria and proteinuria on urinalysis and creatinine rising to a maximum of 3.64 mg/dL, approximately double her baseline of 1.5-2.0 mg/dL. She was additionally found to have oral ulcers on the hard palate that were not previously noted. She was empirically treated with vancomycin and piperacillin-tazobactam for broad-spectrum coverage of her suspected infection without improvement. CT head and MRI brain performed due to acute change in mental status showed findings consistent with vascular dementia. She received another course of valacyclovir for concern for HSV infection, but HSV 1 and 2 PCR were negative, so this medication was discontinued. Hepatitis B and C antibodies were also negative. MRI of the feet was not concerning for osteomyelitis secondary to gangrenous foot wounds, and biopsy with direct immunofluorescence microscopy was not indicative of vasculitis. Repeat autoimmune studies showed persistently elevated anti-MPO/PR3 antibodies, improving but persistently elevated anti-dsDNA antibody to 562, elevated anti-cardiolipin IgM antibodies, and anti-histone antibody elevated to 3,8 U (strong positive = > 2.5 U). Her C3 complement was low on two occasions to 77 and 79, but C4 complement was within normal limits. Because the consulting rheumatology team had such strong suspicion for a rheumatologic process given her antibody titers, decreased C3, lack of resolution with other therapies, and presenting symptoms, she was started on a course of alprostadil, a vasodilating prostaglandin E1 analog, and 80 mg of IV methylprednisolone daily, which led to improvement of both her bilateral foot wounds and her acute kidney injury as indicated by creatinine returning to her baseline range. The IV methylprednisolone was decreased to 40 mg daily due to upper GI bleed possibly due to bleeding gastric ulcer, but despite this change, her improvement remained steady. A renal biopsy was performed about a week after beginning immunosuppressive therapy which demonstrated findings consistent with diabetic glomerulonephritis and pan-negative immunofluorescence.
DIFFERENTIAL DIAGNOSIS

At the time of presentation, it was suspected that Mrs. J’s toxic metabolic encephalopathy was due to an infection of her bilateral gangrenous foot wounds with possible osteomyelitis and worsened by her concurrent vascular dementia. Given her history of positive p-ANCA, anti-dsDNA, and anti-histone antibodies, lack of improvement on antibiotics, negative imaging studies for osteomyelitis, and concurrent acute kidney injury on chronic kidney disease that was refractory to fluid boluses and markedly improved along with healing of bilateral foot wounds with corticosteroids and alprostadil respectively, it is far more likely that the primary disease process leading to her worsening clinical presentation was rheumatologic in nature. It is also important to note that it is likely that her overall clinical presentation was exacerbated as a result of several disease processes acting in tandem with one another, including rheumatologic disease, T2DM, peripheral vascular disease, and chronic kidney disease.

Given that Mrs. J also met both EULAR/ACR and SLICC criteria for SLE with her positive ANA, positive anti-dsDNA antibodies (95% sensitivity for SLE), and oral ulcers, late-onset SLE was at the top of our differential diagnosis despite her negative biopsy results. Anti-histone antibodies are commonly thought to be associated primarily with drug-induced lupus; however, their presence has been noted in up to 75% of both drug-induced and primary SLE. Additionally, anti-dsDNA antibodies are seen in more than 50% of SLE cases but only up to 5% of drug-induced lupus cases.

On the other hand, her history of hydralazine-use with decreasing anti-dsDNA antibody titers in the few weeks following cessation of the drug would suggest the possibility of a hydralazine-induced ANCA vasculitis versus lupus, given that drug-induced rheumatologic diseases typically have a resolution of findings within weeks to months of drug cessation. Drug-induced lupus and SLE are not always distinguishable based on clinical presentation and pharmacologic therapies tend to be similar when required; the hallmark of drug-induced lupus is that it would resolve with cessation of the drug. In this case, it is difficult to determine whether her condition improved from cessation of hydralazine, initiation of corticosteroids, or a combination of the two given the timeline of her clinical course. Based on her clinical presentation, the severity of her symptoms would point more towards primary disease, given that neither drug-induced lupus nor ANCA vasculitis tend to present with organ involvement. It is also important to note that her comorbid conditions likely played a role in the severity of her presentation, making severity of presentation a less reliable parameter due to confounding.

Lastly, without a renal biopsy confirming classic pathologies of either SLE, such as “full-house” staining for immunoglobulins and complement, or ANCA vasculitis, such as pauci-immune crescentic glomerulonephritis, it is difficult to distinguish between these two pathologies based on clinical presentation and laboratory findings alone. Positive ANCA serologies are associated with both ANCA vasculitis, and up to 20% of patients with SLE also have positive ANCA on serologic studies. This patient’s extrarenal manifestations are similarly minimally helpful in differentiation between the two. For example, she has interstitial lung disease (ILD) that was diagnosed only a year prior to her current presentation, but this disease has been associated with both ANCA vasculitis and SLE. This finding is also confounded by the fact that she formerly used tobacco products, which may also lead to interstitial lung disease.

OUTCOME & FOLLOW-UP

Despite the biopsies being negative, given her clinical presentation and improvement on immunosuppressive therapy, she was discharged back to the outpatient rehabilitation facility with a steroid taper, mycophenolate mofetil for long-term immunosuppression and plans to follow up with rheumatology as an outpatient in two weeks.

DISCUSSION

Although Mrs. J presented with many symptoms concerning for possible sequelae of her prior-known medical problems, such as her peripheral vascular disease and T2DM, a bird’s eye view of her constellation of symptoms makes it clear that there was a rheumatologic process that was largely confounded by her other medical problems, irrespective of whether it was primary or induced by hydralazine use. Her case provides an opportunity to explore setting a precedent for determining whether the etiology of a patient’s rapidly declining clinical presentation is rheumatologic in nature. In patients with persistently worsening multiorgan disease and new findings classically associated with rheumatologic disease, such as mucocutaneous ulcers, a rheumatologic workup is warranted to rule out the possibility of new-onset rheumatologic disease. Additionally, this case presents an opportunity to stress the importance of a thorough history and physical exam in order to determine appropriate interventions as early as possible in the disease course.

One of the most intriguing aspects of this case, and simultaneously one of the most prominent limitations, is the lack of findings consistent with rheumatologic disease on biopsy of both the foot and the kidney, with the kidney being of particular interest. It is difficult to determine
whether the lack of findings consistent with lupus nephritis or vasculitis on renal biopsy are due to true lack of renal involvement, presence of long-standing comorbid diabetic glomerulonephritis confounding the biopsy results, or initiation of immunosuppressive therapy prior to renal biopsy. Despite this limitation, Mrs. J’s presentation was likely still primarily rheumatologic in nature given that although diabetic glomerulosclerosis can lead to chronic kidney disease, a rapid deterioration of kidney function is not typical and should be a warning sign that there may be a secondary etiology at play.6

The major question that remains is whether a renal biopsy would reliably show manifestations of a more acute rheumatologic process on top of her existing diabetic glomerulosclerosis, irrespective of prior immunosuppressive therapies. Given that it is widely accepted that renal biopsy is the gold standard for diagnosis of both lupus nephritis and renal vasculitis, there is a lack of literature describing cases in which patients had primary or drug-induced lupus or vasculitis with negative renal biopsy, as well as a predominance of literature describing similar cases with diagnostic renal biopsies. In one retrospective study of 12 patients with diagnosed drug-induced ANCA vasculitis, all 6 patients who had renal biopsies showed the classic pauci-immune crescentic glomerulonephritis.5 Similarly, a recent review of evidence for utility of renal biopsy in patients with lupus nephritis found that the presence of two, three, or four of the five commonly encountered pathologic findings on renal biopsy of lupus nephritis had specificities of 0.89, 0.95, and 0.98, respectively, and sensitivities of 0.92, 0.80, and 0.66, respectively.7 These criteria include intense C1q staining, full-house staining, extraglomerular deposits, tubuloreticular inclusions, and combined subendothelial and subepithelial deposits, none of which Mrs. J’s renal biopsy revealed.7

The assertion that patients with drug-induced lupus or vasculitis should have findings consistent with such diagnoses on renal biopsy seems contrary to the notion that it is quite rare for these conditions to have extensive renal involvement, especially given that resolution often begins after cessation of the offending drug.3 4 An argument against such an assertion could be made based on the clinical correlate of the approach to biopsy for giant cell arteritis after corticosteroid initiation. For giant cell arteritis, evidence suggests that temporal artery biopsy can be performed up to four weeks after starting high-dose corticosteroids without degradation of the accuracy of the study.10 If we choose to use this as a model for our case, it stands to reason that if administration of the offending drug is ceased and immunosuppressive therapy is begun prior to renal biopsy, it becomes less likely that consistent findings will be seen on biopsy, with the accuracy of the results being significantly affected after some unknown time period.

KEY POINTS

- Unlike primary rheumatologic disease, drug-induced rheumatologic disease tends to have less severe presentation than primary rheumatologic disease and typically resolves with cessation of the offending medication.
- Comorbid medical conditions can convolute the diagnosis of an underlying rheumatologic disorder based on severity of symptoms and organ involvement alone.
- Although renal biopsy is the gold standard of diagnosing both lupus nephritis and renal vasculitis, further research is needed regarding whether clinical judgement should be used in cases when renal biopsy is negative but clinical presentation is consistent with rheumatologic disease.

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A Severe Case of Hypertriglyceridemia in Alcoholic Hepatitis

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CASE DESCRIPTION

A 53-year-old man with a past medical history of hypertension and alcohol abuse with prior episodes of alcoholic hepatitis presented to the hospital with generalized weakness. He was in his usual state of health until 4 days prior to admission when he began to develop generalized weakness, nausea, and vomiting. Notably, he had had multiple prior admissions with similar symptoms attributed to hyponatremia. He endorsed drinking a few beers daily but denied any other drug use. Review of systems was otherwise negative.

On physical exam he was comfortable appearing and was in no acute distress. Vital signs were within normal limits. Heart and lung sounds were normal, abdomen was soft and nontender, and he had no peripheral edema. He did have scleral icterus, but no jaundice or pruritus. Initial lab testing yielded a high volume of milky white serum (Figure 1), which could not be run on the hospital’s lab equipment. The blood work was sent to another facility with the appropriate centrifuge.

His admission labs were significant for a sodium of 110 mmol/L and a triglyceride level of 2014 mg/dL, which during the admission peaked at 3025 mg/dL. His liver function panel was notable for a total bilirubin level of 6.3 mg/dL, AST 174 IU/L, ALT 81 IU/L, and ALP 910 IU/L.

Following a diagnosis of hypertriglyceridemia, the patient was admitted to the ICU and treated with an insulin drip, high dose statin, niacin, and omega-3 acids (Lovaza). His triglyceride level upon discharge was 224 mg/dL. His hyponatremia (which was present on admission despite correction for triglycerides) improved with fluids. GI was consulted for his abnormal liver function tests. He underwent MRCP which was normal, and immune/viral serologies were also within normal limits. The ultimate cause of all of his lab abnormalities was thought to be alcohol use and alcoholic hepatitis. His labs were normal at his follow up appointment two weeks after discharge.

Figure 1. Initial blood samples drawn from patient yielded milky white serum. Samples required send out to hospital with appropriate centrifuge for isolation of serum.
DISCUSSION

Normal triglyceride levels are typically in the <150mg/dL range, and in cases of hypertriglyceridemia levels typically remain <1000 mg/dL. Untreated, hypertriglyceridemia can cause coronary atherosclerosis and acute pancreatitis, which can be a medical emergency. In severe cases, plasmapheresis may be employed to rapidly decrease serum triglyceride levels and reduce organ damage. Initial workup of patients with hypertriglyceridemia may be delayed as a high level of lipids in the plasma (which appear as a characteristic milky white serum) interferes with the analysis of common lab tests, often requiring ultracentrifugation for isolation of serum. In this case, the patient presented with a triglyceride level >2000 mg/dL however in the absence of severe sequelae such as acute pancreatitis the typical approach of insulin, statins, niacin, and omega-3 fatty acids was employed instead. This patient’s hypertriglyceridemia was likely caused by severe alcohol abuse, as high levels of alcohol both increase triglyceride production and decrease levels of lipolysis.

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Opioid-Induced Secondary Adrenal Insufficiency in a Young Patient with Chronic Pancreatitis

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INTRODUCTION

Opioid misuse is a national public health crisis that has contributed to a decrease in life expectancy in men and women in the US. From 1999-2017, the rate of drug overdose deaths tripled, largely due to the rise in opioid use. Despite widespread misuse, chronic opioid therapy still has a role in the clinical setting. Adverse effects include dizziness, nausea, vomiting, respiratory depression, and dependence. While these side effects are well-documented, other effects of opioids are less explored, including opioid-induced adrenal insufficiency. The typical presentation of adrenal insufficiency from any cause can include fatigue, nausea, vomiting, weight loss, abdominal pain and muscle aches. Laboratory findings might include hyponatremia and hyperkalemia. This case, however, presents a patient with atypical presentation but confirmed diagnosis of adrenal insufficiency in the setting of chronic opioid use. Ultimately, given chronic opioid use both prescribed and unprescribed, it is imperative that healthcare providers understand the endocrine effects of opioids as adrenal insufficiency is associated with higher morbidity and mortality.

The adrenal gland is made up of a cortex and medulla which each produce vital hormones. Specifically, the cortex is responsible for producing glucocorticoids, mineralocorticoids, and androgens. Destruction or dysfunction of the adrenal gland may lead to deficiency of these hormones. Adrenal insufficiency can be classified into primary, secondary, or tertiary types. Primary adrenal insufficiency denotes malfunctioning of the adrenal gland itself. Secondary adrenal insufficiency is characterized by a decreased level of adrenocorticotropic hormone (ACTH) released by the pituitary gland. Tertiary adrenal insufficiency is defined by a decreased level of corticotropin-releasing hormone (CRH) from the hypothalamus. Opioids bind to mu, kappa, and delta opioid receptors to create effects throughout the body, including on the hypothalamus and pituitary. This is the proposed mechanism for opioid-induced suppression of the hypothalamus-pituitary-adrenal (HPA) axis noted in some studies.

NARRATIVE

A 33 year-old man with a past medical history of chronic pancreatitis secondary to heavy alcohol use presented to the hospital with a chief complaint of abdominal pain, nausea, vomiting, and poor appetite. During the hospitalization, the patient was hydrated with intravenous fluids and pain control was optimized. Since his initial diagnosis of pancreatitis, his home analgesics included oxycodone 10 mg, gabapentin 800 mg and duloxetine 60 mg. On admission his oxycodone was discontinued and he was started on hydromorphone through a patient-controlled analgesia pump as well as a ketamine infusion titrated by an acute pain management team. During endoscopy to perform a celiac plexus nerve block, findings consistent with chronic calcific pancreatitis were noted. With this procedure, his pain was better controlled and he was transitioned back onto an oral opioid-containing pain control regimen with oxycodone 10 mg, gabapentin 900 mg, and duloxetine 60 mg. However, his hospital course was further complicated by uncontrolled hypertension and fluctuating blood sugars.

His blood glucose readings were initially as high as 500 mg/dL, at which point an insulin infusion was initiated for better control. The patient did not have evidence of diabetic ketoacidosis. The infusion was eventually discontinued and the patient was transitioned to a basal bolus insulin regimen.

The patient’s blood pressure was also difficult to control. His home medications included carvedilol 3.125 mg, hydralazine 100 mg, nifedipine 60 mg, losartan 100 mg, and a clonidine patch 0.3 mg. Due to his inability to tolerate medications by mouth secondary to nausea, the patient was taking these medications inconsistently.

Although his poorly controlled blood sugars and pressures were thought to be in part due to his abdominal pain, a secondary workup was pursued, especially considering his extensive multi-drug regimen. This workup included an aldosterone-renin ratio, urine and serum metanephrines, and a morning cortisol level. Due to hypertension and hyperglycemia, as well as normal serum sodium (136 mmol/L) and potassium (4.0 mmol/L), suspicion for adrenal insufficiency was low. However, the morning cortisol level was low at 2.3 mcg/dL. A cosyntropin stimulation test confirmed adrenal insufficiency; cortisol levels only increased to 10.8 mcg/dL after 60 minutes. A baseline ACTH level was found to be low at <9 pg/mL. Other lab findings were significant for normal values of sodium (136 mmol/L) and potassium (4.0 mmol/L). Since this was a surprising finding given the lack of clinical signs and symptoms of adrenal insufficiency, the stimulation test was repeated with similar results. The patient was...
started on prednisone 5 mg daily and instructed to follow up with Endocrinology within 2 months to repeat a cosyntropin stimulation test to reassess his hypothalamic-pituitary-adrenal (HPA) axis. The leading differential of this atypical presentation of secondary adrenal insufficiency was thought to be due to his history of chronic opioid use.

**DISCUSSION**

Opioids have widespread effects on the body, but their impact on the HPA axis is not well understood. There have been a few studies and case reports that have demonstrated opioid-induced adrenal insufficiency. One review concluded that 9% to 29% of patients receiving long-term opioids develop adrenal insufficiency. Two clinical trials showed that treatment with naloxone, an opioid antagonist, led to increased cortisol levels and an augmented response to corticotropin-releasing hormone (CRH). These findings suggest that opioids suppress the hypothalamic-pituitary-adrenal axis. Animal studies have shown mixed findings in regards to the effect of opioids on the HPA axis. In two animal studies, a single injection of morphine led to increased levels of corticotropins and glucocorticoids. In contrast, long-term administration of opioids had variable effects on the HPA axis in rats. One study showed low doses of intraperitoneal morphine demonstrated adrenal insufficiency in rodents, whereas rats treated with increasing doses of intravenous morphine (10-100 mg/kg) twice a day for 16 days were found to have elevated corticosterone levels. While most human studies have shown suppression of the HPA axis in the setting of chronic opioid use, one study analyzing 39 patients with chronic opioid use showed hyperfunctioning of the HPA axis. Individual differences in the impact of chronic opioid use on the HPA axis may be attributed to variation in opioid receptor polymorphism that may alter affinity.

This is a unique case of opioid-induced adrenal insufficiency because the patient lacked the classic lab findings associated with adrenal insufficiency including hypotension, hyponatremia, hyperkalemia, and/or hypoglycemia. In fact, he was persistently hypertensive and hyperglycemic. The most common etiology of secondary adrenal insufficiency is exogenous glucocorticoids. Our patient had no history of glucocorticoid use. Treatment of opioid-induced adrenal insufficiency includes glucocorticoid administration. Case reports have shown that discontinuation of opioids may reverse the adrenal insufficiency. Because there are currently no screening guidelines for adrenal insufficiency in patients with chronic opioid use, this endocrinopathy is likely underreported. This case highlights the notion that the clinical presentation of adrenal insufficiency may not always manifest with the classic signs of hypoadrenalism. However, it is critical that this effect of opioids is considered given that the clinical manifestations of adrenal insufficiency may be masked by concurrent illness

**CONCLUSION**

Chronic opioid use is common, and may be underreported by patients due to non-prescription use. In addition to many well-known risks of chronic opioid use, opioids can affect the HPA axis. Healthcare providers and patients should be alert for the possibility of adrenal insufficiency with long-term use of opioids. Adrenal function should be monitored in these patients, and glucocorticoids should be administered whenever necessary.

**REFERENCES**

A Slow Burning Diagnosis: A Case Report of Hemophagocytic Lymphohistiocytosis Preceding the Diagnosis of Subcutaneous Panniculitis-Like T-Cell Lymphoma

Steven Manobianco, MD, William Bradford, MD, Ida Micaily, MD, Adam Binder, MD

INTRODUCTION

HLH is a severe inflammatory syndrome characterized by primary or secondary immune dysregulation causing excess activation of macrophages and cytotoxic lymphocytes, leading to multi-system dysfunction. Diagnosing and managing HLH can be challenging for clinicians, with HLH-2004 criteria for diagnosis requiring a molecular diagnosis or the presence of at least five of the following: fever, splenomegaly, cytopenia involving two or more cell lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen or lymph nodes with no evidence of malignancy, low or no NK cell activity, elevated ferritin, or elevated soluble IL-2 receptor. These criteria have been utilized to develop the HScore, a tool used to assist in determining the probability of HLH based on the aforementioned abnormalities. After diagnosis, treatment typically includes chemotherapy and immunosuppression, followed by allogeneic bone marrow transplant.

CASE PRESENTATION

A 27-year-old Vietnamese female with no past medical or family history presented to the emergency department with three weeks of intermittent fevers, headache, and unilateral neck swelling. She immigrated to the United States from Vietnam five years prior. She denied any recent travel, environmental exposures, sick contacts, or chronic medications. She denied shortness of breath, cough, nausea, vomiting, or diarrhea.

On examination, temperature was 39.2°C, heart rate 110 beats per minute, blood pressure 112/74 mmHg, respiratory rate 16 breaths per minute, and oxygen saturation 96% on room air. Scleral icterus was absent. She was tachycardic with regular cardiac rhythm, and lungs were clear to auscultation bilaterally. Two mobile, non-tender, left-sided cervical lymph nodes measuring 1-2cm each were palpated without further lymphadenopathy. Her abdomen was non-tender, non-distended, and normoactive. Her skin was dry, without rashes, petechiae, or ecchymoses.

Initial laboratory workup was notable for a hemoglobin of 8.4 g/dL, white blood cell count of 2.9 B/L with normal differential, aspartate aminotransferase (AST) of 308 IU/L, and alanine aminotransferase (ALT) of 248 IU/L. Chest radiography was negative for any acute process. Computed tomography of the neck, chest, abdomen, and pelvis noted trace pleural effusions, abdominopelvic ascites, hepatosplenomegaly, and diffuse colitis. Blood and urine cultures (including acid fast and fungal cultures) showed no growth.

A comprehensive infectious, hematologic, and rheumatologic workup was performed, including mycobacterial, fungal, malarial, and zoonotic testing; invasive studies included lumbar puncture, paracentesis, cervical excisional lymph node biopsy, liver biopsy, and laparoscopy with mesenteric and lymph node biopsy. There was no evidence of active acute infection, malignancy, or autoimmune disease on serologic testing. Liver biopsy showed chronic hepatitis with minimal-mild activity and no fibrosis. Peritoneal fluid showed reactive mesothelial cells without evidence of malignancy, and fluid cultures were negative. Mesenteric and lymph node biopsy showed benign lymph nodes with reactive sinus histiocytosis and focal necrosis; acid fast and fungal stains were negative. Bone marrow biopsy and peripheral flow cytometry revealed a hypercellular bone marrow with trilineage hematopoiesis, occasional hemophagocytosis, adequate iron, and no evidence of leukemia/lymphoma. Findings were discussed with hematopathology and medical oncology services, and ultimately felt to be inconclusive. She was discharged home with ongoing fevers but clinically stable, with plans for outpatient follow-up.

Four months after discharge, she presented again with nausea, vomiting, and fever. She reported returning to Vietnam and being hospitalized there with similar but worsening symptoms. A diagnostic workup from that hospitalization, including bone marrow biopsy, was unrevealing. She reported generalized myalgias, epistaxis, malaise, and abdominal pain. On exam, temperature was 40.6°C, heart rate 105 beats per minute, blood pressure 90/64 mmHg, respiratory rate of 25 breaths per minute,
and oxygen saturation 95% on room air. Physical exam noted scleral icterus. She had sinus tachycardia, and lungs were clear to auscultation bilaterally. Her abdomen was diffusely tender to palpation with guarding, and her liver edge was palpable. Ecchymoses were present diffusely, and crusted blood was visualized in the nares. Labs were notable for Hgb 8.6 g/dL, WBC 6.8 B/L with 86% neutrophils, platelets 35 B/L, AST 3200 IU/L, AST 680 IU/L, triglycerides 273 mg/dL, ferritin 75910 ng/dL, fibrinogen 40 mg/dL, and IL-2R of 30470 pg/mL; total HScore was 299. After receiving steroids, intravenous fluids, and broad-spectrum antibiotics, she was admitted to the medical intensive care unit and initiated on dexamethasone and etoposide per the HLH-94 protocol with improvement in her clinical condition. She was discharged home two weeks later, successfully completing a taper of dexamethasone and weekly etoposide infusions with her oncologist. Approximately eight months after discharge, she was seen by Dermatology for erythematous firm plaques with ulceration on her thigh that persisted for several months despite oral antibiotics. She underwent punch biopsy of the lesion twice; her first biopsy was inconclusive, and second biopsy demonstrated subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with immunohistochemistry showing the beta T-cell phenotype.

DISCUSSION

The non-specific components of the HLH-2004 criteria, combined with an often-severe clinical presentation, create a unique challenge for clinicians to differentiate HLH from other critical illnesses; for example, data on malignancy-associated HLH suggests that less than 50% of patients promptly received HLH-directed therapy due to diagnostic difficulty. As such, early recognition of HLH is critical. With increasing recognition and diagnosis of adult HLH, there is greater understanding of disease characteristics and how varying etiologies influence patient outcomes. Although adult treatment protocols are derived predominantly from pediatric data, new clinical trials have the potential to change future management of adult HLH, with drugs targeting INF-γ, CD-52, IL-1, and JAK-STAT in varying stages of testing. In adult patients with newly diagnosed HLH, secondary HLH remains significantly more common than primary HLH. While the most common etiology varies geographically, lymphoma represents the most common malignancy-related cause and overall secondary cause of HLH. Since its initial description, SPTCL has been closely linked to hemophagocytic syndromes. Representing approximately 1% of non-Hodgkin’s lymphomas, it is highly associated with a rapidly progressive course of HLH. Flow cytometry differentiates the κβ (SPTCL-AB) or γδ (SPTCL-GD) T-cell phenotypes, with SPTCL-AB usually following a more indolent course and conferring a better prognosis. Treatment of SPTCL is variable but often includes steroids, other immunosuppressive agents, or cytotoxic chemotherapy.

A final diagnostic challenge was her clinical stability without disease progression over several months; findings such as colitis and regional lymphadenopathy initially suggested other causes. Despite her high HScore, it was challenging to definitively rule out infectious causes and commit her to cytotoxic therapy. Similar diagnostic dilemmas are likely responsible for the delayed diagnosis and treatment widely noted in other studies. As such, practitioners should have high clinical suspicion for secondary HLH in adult patients with appropriate disease markers and strongly consider workup for underlying malignancy.

CONCLUSION

As evidenced in this case, HLH is an uncommon syndrome that can be challenging to differentiate from other conditions causing multi-organ system dysfunction. Secondary HLH is significantly more common than primary HLH in adult patients, and malignancy (especially lymphoma) is the most common secondary etiology. Due to the non-specific diagnostic criteria for HLH and intense cytotoxic therapy, many patients experience delays in diagnosis and treatment.

REFERENCES

A Rare Presentation of a Clear Cell Variant of Peritoneal Mesothelioma

Nivethietha Maniam, MD, Michael Lee, MD, Mihir M. Shah, MD, H Richard Alexander, MD

ABSTRACT

Primary malignant peritoneal mesothelioma with clear cell subtype is a rare malignancy with few previously reported cases. We present a 63-year-old female who presented with abdominal distention and was diagnosed with clear cell mesothelioma of the peritoneum with an isolated metastasis to the liver. The patient underwent surgical resection of a greater than 50 cm mass with en-bloc partial liver and gastric resection with an uneventful post-operative course. There are established prognostic and treatment recommendations for peritoneal mesothelioma based on histological subtype and patient-specific factors, although they do not explicitly incorporate clear cell subtype. This case report describes the presentation, treatment and early outcome of a rare form of peritoneal mesothelioma.

INTRODUCTION

Primary malignant peritoneal mesothelioma is a rare malignancy. Clear cell subtype of the epithelioid variant is even rarer, with very few cases reported in the literature. In this case we present a 63 year-old female who presented with abdominal distention, who was found to have primary malignant peritoneal mesothelioma of clear cell subtype with hepatic metastases who ultimately underwent surgical resection with plan for adjuvant chemotherapy. Due to the lack of a well-defined presentation pattern or therapeutic strategy for this specific subtype, it is important to report this case and its outcomes.

CLINICAL SUMMARY

The patient is a 63 year-old female who presented with a 6-month history of gradually increasing abdominal girth, discomfort, and early satiety. She underwent esophagogastroduodenoscopy and colonoscopy, which were found to be normal. On abdominal computed tomography she was found to have an intra-abdominal mass 26 cm in size that appeared to be arising from the epigastrium and a 5cm centrally located hepatic mass consistent with solitary hepatic metastasis (Figure 1). The abdominal mass appeared to be encapsulated and there was no evidence of diffuse disease in the peritoneal cavity. The patient underwent a percutaneous biopsy of the mass with histopathology diagnosing as clear cell mesothelioma. On immunohistochemical staining, the tumor was positive for AE1/AE3 and CK7 suggesting an epithelial neoplasm and positive for calretinin, CK/CK6, and WT-1. It was negative for colorectal, GIST, hepato-cellular, mullerian and renal tumor markers. The pathology was reviewed at two centers with concordant impressions. Given the histology, the patient was scheduled for a laparotomy and resection of her abdominal mass.

Figure 1. Axial (a) and coronal (b) abdominal computed tomography illustrating an intra-abdominal mass approximately 26cm in size that appeared to be arising from the epigastrium and a 5cm centrally located hepatic mass consistent with solitary hepatic metastasis.
On admission, she was noted to have leukocytosis to 16,100/μl and found to have a urinary tract infection, which was treated with a regimen of levofloxacin. She was anemic with a hemoglobin of 7.3g/dl, a platelet count of 830,000/μl, a prothrombin time of 18.7 seconds, an albumin of 3.1g/dl, and prealbumin of 7.2mg/dl. On hospital day two, the patient underwent surgical resection. During the procedure, the mass was found to be greater than 50 cm in diameter, filling the entire abdomen and appeared to be arising from the greater omentum and distal stomach. The mass was densely adherent to and infiltrating the capsule of the left lateral segment of the liver and adherent to but not infiltrating the transverse colon (Figure 2). A distal gastrectomy and partial hepatectomy were performed en bloc with the mass and a Roux-en-Y gastrojejunostomy was performed. The liver lesion was left in situ given its central location and there was no evidence of any other peritoneal dissemination.

The patient required one unit of packed red blood cells with an adequate response and otherwise had an uncomplicated post-operative course with normalization of her leukocytosis. She was discharged on post-operative day seven. Pathology of the resected specimens confirmed clear cell malignant mesothelioma with negative surgical margins. Upon recovery, the liver metastasis will be restaged and treated with systemic or regional therapy.

DISCUSSION

Malignant mesothelioma is a rare malignancy of the serosal membranes of the pleura, peritoneum, pericardium, or tunica vaginalis testes. There are only 3300 cases of mesothelioma diagnosed in the United States every year, with only 10 to 15 percent peritoneal in etiology.\textsuperscript{4} Tumors derived from the serosal membranes often grow in a variety of histologic patterns. According to their light microscopic appearance, mesotheliomas have been subdivided into epithelioid, sarcomatoid, mixed epithelioid and sarcomatoid (biphasic), and desmoplastic subtypes. The most frequent histologic type of malignant mesothelioma is epithelioid. While epithelioid mesotheliomas usually have a tubulopapillary, adenomatoid, or solid pattern, on rare occasions they may also present with other histologic patterns including deciduoid, pleomorphic, small cell, signet-ring, as well as clear cell which is characterized by cells with cytoplasmic clearing usually caused by the accumulation of large amounts of intracytoplasmic glycogen.\textsuperscript{5,7}

Predominately clear cell mesothelioma is an especially rare finding with fewer than 30 cases reported in the literature, and even rarer to present specifically in the peritoneum, with only one previous case reported in the peritoneum of a female patient.\textsuperscript{1,3,5,7} While the tumor can occur in children and young adults, it is usually found in older adults. Males and females are equally affected, however males are at a higher risk due to increased occupational exposure.\textsuperscript{4} While the etiology of malignant clear cell mesothelioma is unknown, it has been associated with asbestos exposure, radiation treatment, and mutations in the BAP1 gene.\textsuperscript{8} The symptoms can often be unspecific and depend on the size and location of the tumor. Small sized tumors may be asymptomatic during the initial stages of tumor growth while large-sized tumors can present with pain, obstructive symptoms, fatigue, and weight loss. Our patient presented with relatively mild symptoms that appeared to be caused by compression rather than infiltrative effects and she continued to maintain an excellent performance scale with an ECOG score of 1 despite the size of the mass in her abdomen.

In order to diagnose clear cell mesothelioma in our patient, an initial diagnosis was made after a complete evaluation of the patient’s history and physical along with an abdominal CT scan. While imaging tools such as CT, MRI, and PET scan may reveal the presence of a tumor, a tissue biopsy is necessary to make a definitive diagnosis. The differential diagnosis for malignant mesothelioma depends on the predominant histologic category. Most tumors are a mixture of more than one cell type; therefore, due to the rarity of clear cell mesothelioma this diagnosis can often be missed. While immunohistochemical staining plays an important role...
in the workup of malignant mesothelioma, IHC varies depending on the histological type of mesothelioma, the location of the tumor, and the type of tumor being considered in the differential diagnosis. These variants can often be confused with a variety of other neoplastic conditions with a similar clear cell morphology. In our case this patient’s diagnosis was confirmed by immunohistochemical studies which demonstrated reactivity for calretinin, keratin 5/6, and WT1, an important pattern that is characteristic of mesothelioma. Calretinin is demonstrated in nearly all epithelioid mesotheliomas, keratin 5/6 is expressed in 75%-100% of mesotheliomas, and approximately 70%-95% of mesotheliomas show nuclear positivity for WT1. In addition, we were careful to rule out other causes of clear cell tumors. The diagnosis of epithelioid mesothelioma with clear cell morphology can often be difficult as it must be differentiated from clear cell renal cell carcinomas, clear cell carcinomas of the lung, clear cell melanoma, and other clear cell tumors that can metastasize to the pleura or peritoneum. Therefore, immunohistochemical panels should contain both positive and negative markers for mesothelial differentiation and for neoplasms considered in the differential diagnosis.

Clear cell mesothelioma is a highly aggressive cancer that requires a multidisciplinary approach. The prognosis for malignant peritoneal mesothelioma is relatively poor due to organ dysfunction, local invasion and metastasis, and the high rate of recurrence. Stage and histology are the strongest prognostic factors among patients with mesothelioma, with sarcomatoid and biphasic histologic subtypes having worse outcomes compared with epithelioid mesothelioma. In addition to size, stage, and grade of the tumor, prognosis generally depends on a combination of factors including age, overall health of the patient, cell growth rate, and response to treatment.

The European Organization for Research and Treatment of Cancer (EORTC) has developed prognostic scoring systems for peritoneal mesothelioma. They reviewed data from 204 adults with malignant peritoneal mesothelioma and when five factors were taken into consideration (poor performance status, high white blood cell count, male gender, sarcomatous subtype, and the certainty of the diagnosis), a low risk group with a prognostic score of 0–2 poor prognostic factors and a high risk group with >3 prognostic factors were found to have a one-year survival rates of 40 and 12 percent, respectively. Median survival from the date of study entry was 8.4 months. Similarly, the Cancer and Leukemia Group B (CALGB) evaluated 337 patients with malignant mesothelioma and found that pleural involvement, increased serum LDH, poor performance status, chest pain, increased platelet count, non-epithelial histology, and age older than 75 years predicted poor survival. These factors were differentiated into six prognostic subgroups with median survival times ranging from 1.4 to 13.9 months with a median survival overall of seven months. Using these scoring systems our patient fell into the low risk subgroup with a 40% survival rate of one year and a mean survival rate of 9 months. Though our patient was older with a high-grade, bulky tumor, due to her previous good health and the resectability of her tumor given the encapsulated nature of the tumor, we determined that she was a good candidate for surgery. We hope that this case demonstrates the importance of recognizing clear cell variant mesothelioma early and understanding predictive prognosis given individual patient characteristics. Through early detection, we can avoid complications and help increase positive outcomes.

REFERENCES

HEMATOLOGY & ONCOLOGY

A Case of Refractory Gestational Trophoblastic Neoplasia requiring Hysterectomy after Methotrexate

Ida Micali, MD, Saveri Bhattacharya, DO, Russell J. Schilder, MD

INTRODUCTION

Gestational trophoblastic neoplasia (GTN) refers to a group of malignant conditions that develop due to abnormal fertilization causing abnormal proliferation of tissue. GTN is primarily treated with surgical evacuation of the underlying proliferative tissue. Approximately half of cases of GTN arise from molar pregnancy. GTN include invasive moles, choriocarcinomas, placental-site trophoblastic tumors and epithelioid trophoblastic tumors. The most common risk factors associated with GTN are prior molar pregnancy, advanced maternal age (>40 years of age), and Asian and Native American ancestry. Following evaluation of a molar pregnancy, a post-molar GTN is diagnosed based on the International Federation of Gynecology and Obstetrics (FIGO) criteria, which includes elevated human chorionic gonadotropin (hCG) levels, hCG levels increasing >10% across three values recorded over a two-week duration, weekly hCG level plateauing (remaining within +/- 10% of the previous week’s results) over a three-week period, and persistence of detectable serum hCG for more than six months after molar evacuation. A pathologic diagnosis of prior molar pregnancy by curettage with increased hCG levels also would be acceptable for diagnosis. According to the World Health Organization scoring system of GTN, factors including age, antecedent pregnancy, interval months from index pregnancy, pretreatment hCG, largest tumor size, site and number of metastases and previous failed chemotherapy help stratify the risk of patients and determine the type of treatment.

CASE REPORT

A 30 year-old female with a history of hypertension and chronic sinus tachycardia was found to have a complete molar pregnancy at the time of her 8-week ultrasound. A subsequent D&C was performed, and D&C pathologic findings demonstrated an invasive mole. She was found to have a hCG level of 7,000. One week later, her hCG was 15,387. The following week, her hCG was found to be 23,883. A pelvic ultrasound demonstrated findings consistent with thickened, heterogeneous and hypervascular endometrium with cystic areas, consistent with possible residual or recurrent molar pregnancy; however, a mass was never seen on imaging. Given her pathologic findings and serum values, she was classified as a low-risk GTN. Between July 2018 to August 2019, she was treated for her low-risk GTN with a regimen including methotrexate (MTX) 80 mg SQ three days a week alternating with leucovorin. She completed 19 cycles of methotrexate and achieved normalization of hCG levels with 3 normal values recorded (table 2).

However, increasing hCG levels two months after cessation of methotrexate led to concern for residual disease. As such, she was referred to our center for a second opinion. She was classified as FIGO stage I with a WHO score of 6 points, due to: time frame of 12 months since index pregnancy, baseline hCG and previous utilization of single drug (table 1). Her serum hCG increased to 110, leading to the resumption of MTX. She initially responded well to retreatment with MTX, demonstrating undetectable hCG levels for almost three months. After three months, her hCG again began to increase while on treatment (table 2). Possible treatment options at that point included actinomycin-D, EMA/CO, avelumab and radical hysterectomy. The patient had completed child bearing and elected to undergo a radical abdominal hysterectomy - bilateral salpingectomy. Post-surgical pathology ultimately demonstrated a gestational trophoblastic tumor, most consistent with choriocarcinoma invading into the myometrium. Her post-operative HCG was undetectable.

Table 1: Staging & Prognostication

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Disease confined to uterus</td>
</tr>
<tr>
<td>II</td>
<td>GTN extends outside of uterus but is limited to the genital structures (adnexa, vagina, broad ligament)</td>
</tr>
<tr>
<td>III</td>
<td>GTN extends to lungs without known genital tract involvement</td>
</tr>
<tr>
<td>IV</td>
<td>All other metastatic sites</td>
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</tbody>
</table>

Table 2: Modified WHO Prognostic Scoring System as Adopted by FIGO

<table>
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<tr>
<th>Score</th>
<th>Age</th>
<th>Interval months from index pregnancy</th>
<th>Pretreatment hCG (log)</th>
<th>Largest tumor size (cm)</th>
<th>Site of metastases</th>
<th>Previous failed chemotherapy</th>
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<td>&gt;12</td>
<td>&lt;10</td>
<td>&lt;3</td>
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DISCUSSION

Complete hydatidiform mole and choriocarcinoma are rare, distinct disease processes with characteristic histologic and clinical features. In North America, there is a 0.1% incidence of molar pregnancy in all pregnancies. Although rare, low-risk GTN due to molar pregnancy is almost always curable with single-agent chemotherapy. A 2016 Cochrane database meta-analysis compared chemotherapy regimens for low-risk GTN and concluded that although pulsed actinomycin-D may achieve high primary cure with less chance of treatment failure in women with low-risk GTN, worsening serious adverse events were seen with this regimen than with a methotrexate regimen. Actinomycin-D (Act D) may be used for patients who cannot tolerate methotrexate due to side effects of hyperemesis, alopecia and tissue extravasation. In a clinical trial in low-risk GTN, patients with a hCG value >4000 IU/L were found to respond poorly to Act D. Alternatively, a study examining 1072 low-risk GTN patients with WHO score <6 demonstrated that hysterectomy as a first-line treatment is effective without salvage chemotherapy in approximately 82% of these patients. However, it was also concluded that young patients, such as the case mentioned above, should be considered for single-agent chemotherapy instead of surgery-only, as chemotherapy has been almost always curative while maintaining fertility.

In high-risk or refractory GTN, consideration can be given to combination chemotherapy with cyclophosphamide and vincristine (EMA/CO). The cumulative 5 year survival rate for these patients is greater than 85%, and patients who developed resistance to this regimen generally were salvaged by further cisplatin-based chemotherapy and surgery. For low risk GTN patients who are resistant to single-agent MTX or Act D, preliminary data from a phase II multicenter, cohort trial investigating the anti-PD-L1 antibody avelumab has shown promise, with 8 out of 15 patients demonstrating 8 months of complete response. Due to this promising data, many ongoing clinical trials in the low-risk GTN population include immunotherapy as a single agent or in addition to MTX (NCT03135769, NCT04303884).

CONCLUSION

Although complete molar pregnancy related GTN is a generally rare condition, low and high-risk tumors have a high cure rate with chemotherapy. In the above case, our patient had low-risk GTN, however, given she had an increase in hCG upon cessation of single-agent methotrexate she had evidence of persistent disease or possible relapse. Treatment options for this included hysterectomy, which the patient elected to undergo. Hysterectomy led to undetectable post-operative HCG levels, and surgical pathology proved that her underlying etiology was choriocarcinoma.

REFERENCES

Idiopathic Retroperitoneal Fibrosis
Candace Derenge, MD

OUTCOME & FOLLOW-UP
The patient was started on high-dose steroids (1mg/kg prednisone daily for 4 weeks), which significantly improved his pain.

DISCUSSION
Idiopathic retroperitoneal fibrosis is a rare diagnosis of exclusion, and our patient provides a classic example. Retroperitoneal fibrosis is 2-3x more common in men and the mean age at onset is 55 to 60. Clinical presentation is back, abdominal, and/or testicular pain, systemic symptoms (e.g. fatigue, weight loss, chills), oliguria from obstructive uropathy, resultant volume overload, and/or claudication. Flank and abdominal pain is the most common symptom of idiopathic retroperitoneal fibrosis, and systemic symptoms are the second most common. Diagnosis of retroperitoneal fibrosis is made on CT or MRI of the abdomen, and diagnosis of idiopathic retroperitoneal fibrosis is made through excluding possibly etiologies through bloodwork and biopsy.

KEY POINTS
Idiopathic retroperitoneal fibrosis is a rare cause of abdominal pain, and it is a diagnosis of exclusion.

REFERENCES
Pancreatic Plasmacytoma: A Rare Extramedullary Manifestation of Multiple Myeloma

Justin Robbins, MD, Greg Habig, MD

Multiple myeloma is a plasma cell dyscrasia in which neoplastic plasma cells pathologically produce monoclonal immunoglobulin and infiltrate bone marrow throughout the skeletal system. The disease is classically characterized by bone pain caused by lytic bone lesions, marked increases in monoclonal antibodies in blood or urine, hypercalcemia, and other systemic signs and symptoms of malignancy including weight loss and night sweats. A rare variant of multiple myeloma presents with extramedullary plasmacytomas, or plasma cell tumors, which arise in organs outside of the bone marrow. The case presented here exhibits this disease variant, with a woman with severe multiple myeloma refractory to multiple treatment modalities who was found to have a pancreatic plasmacytoma.

The patient presented here was a 58-year-old female with a history of refractory multiple myeloma status post autologous stem cell transplant with relapse, hepatitis B virus on entecavir, and recurrent pancreatitis who presented from her outpatient oncology office for evaluation of a transaminitis in the 1000s U/L, and an alkaline phosphatase of 289 IU/L. She was evaluated by gastroenterology with lab work showing reactivation of her hepatitis B, for which she was started on tenofovir. Her hospital course was complicated by acute onset abdominal pain and a worsening alkaline phosphatase in the setting of newly elevated lipase and amylase. She underwent Magnetic Resonance Cholangiopancreatography (MRCP) (Figure 1), which revealed a 1.7 x 1.6 cm mass in the pancreatic head and a 1.9 x 1.7 cm pancreatic tail mass. A fine needle aspiration (FNA) was then performed which showed plasmacytomas at both locations. She was treated with pain control and intravenous fluids for her pancreatitis and evaluated by radiation oncology with plans for outpatient palliative radiation.

Involvement of the pancreas is a rare occurrence in multiple myeloma and is only seen in about 2.3% of autopsies. While its presentation is often asymptomatic, it can present with symptomatology and imaging findings consistent with pancreatitis. The patient described here had recurrent bouts of pancreatitis prior to this hospitalization; however, previous imaging had never shown a mass. It is likely these episodes were in the setting of underlying, undiagnosed malignancy not detected on prior CT scans. Though an uncommon cause, signs of pancreatitis or suspicious pancreatic masses in patients with multiple myeloma should prompt further workup for a possible extramedullary pancreatic plasmacytoma.

REFERENCES

The patient underwent treatment for SARS-CoV-2 pneumonia and rhabdomyolysis with five days of remdesivir, six days of dexamethasone, and intravenous fluids. On hospital day six the patient no longer required supplemental oxygen therapy but experienced a three second pause on telemetry monitoring. The patient left against-medical-advice and re-presented to the ED within 12 hours complaining of new left-sided chest pain. Laboratory results were significant for an initial hs-TnT of 217 ng/L and repeat of 415 ng/L. Electrocardiogram was significant for sinus arrhythmia and acute anterolateral injury pattern with ST-elevations in leads I, aVL, V3-V6 (figure 2). Chest radiograph was significant for vascular congestion in bilateral lung fields (figure 3). Echocardiography was significant for left ventricular ejection fraction of 40-45%, moderate left ventricular dysfunction with peri-apical akinesis. The patient received 324mg of aspirin, 80mg of atorvastatin and was initiated on intravenous heparin therapy. A transfer was initiated to a PCI-capable facility.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included acute ST-elevation myocardial infarction, pulmonary embolism and COVID-19 associated myocarditis.

OUTCOME & FOLLOW-UP

The patient was transferred to the cardiac catheterization laboratory for consideration of emergency coronary angioplasty. Coronary angiogram showed mid left anterior descending (LAD) artery thrombus with 50% stenosis and distal LAD thrombus causing 100% occlusion at the apex (figure 4). No intervention was done as the patient had resolution of his chest pain. The patient was loaded with 180mg of ticagrelor and placed on a tirofiban infusion for 24 hours due to thrombus burden. The patient was maintained on full dose enoxaparin until discharge due to intracoronary thrombus burden then subsequently discharged on dual-antiplatelet therapy, high-intensity statin and lisinopril. As of a six week follow up the patient has been chest pain free and doing well.
Figure 1. 12 lead electrocardiogram: baseline sinus tachycardia.

Figure 2. 12 lead electrocardiogram: anterolateral ST-segment elevation.

Figure 3. Portable Chest Radiograph: vascular congestion in bilateral lung fields.

Figure 4. Coronary angiogram: mid left anterior descending (LAD) artery thrombus with 50% stenosis and distal LAD thrombus causing 100% occlusion at the apex.
DISCUSSION

Acute coronary syndrome (ACS) events are pharmaco-logically treated with platelet inhibition using a loading dose of aspirin, a P2Y12 antagonist, as well as a continuous heparin drip, titrated to maintain full antico-agulation. If the institution’s facilities allow, the patient will be emergently taken to the cardiac catheterization lab to assess ICT burden and intervention via thrombectomy and angioplasty. Facility capabilities, clot burden, and the patient’s overall clinical picture will certainly play a role in management decisions and which treatments are most appropriate for each patient. The most appropriate management depends on patient past medical history, thrombus burden, and overall goals of care. Early and effective interventions are associated with better outcomes.

In our case of a young patient positive for SARS-CoV-2 presenting with ACS, the mechanism of how SARS-CoV-2 can affect ICT should be considered as the precipitating factor and how it may impact our clinical management decisions. SARS-CoV-2 infections are known to create a systemic proinflammatory state which appears to also lead to hypercoagulation and increased thrombus burden in infected patients. An increase in production of inflammatory markers and cytokines in turn increases thrombin production and atherosclerotic plaque instability by increasing the conversion of fibrinogen to fibrin in turn activating platelets thereby promoting clot formation. Moreover, in patients that are critically ill with a SARS-CoV-2 infection can experience dysfunction in their coagulant concentrations thereby leading to disordered development of thrombosis and bleeding called disseminated intravascular coagulation. Sepsis, tachycardia and systemic inflammation can also increase coronary blood flow demand precipitating myocardial ischemia and plaque destabilization.

These proposed mechanisms may have led to our 24 year old patient’s STEMI in the setting of a SARS-CoV-2 infection. There has been an increase in case reports in the literature on ACS and ICT in SARS-CoV-2 positive patients. Knowing the possible risks of hypercoagulation in SARS-CoV-2, recent studies including the "IMPROVEDD Score" create risk stratification scores to determine the need for venous thromboembolism prophylaxis. Similarly, further study is required to guide prevention and management techniques in ICT in patients with SARS-CoV-2 infections.

KEY POINTS

Intracoronary thrombus, COVID-19, Anticoagulation Management, STEMI

REFERENCES

Increasing Patient Confidence in Managing Asthma using Asthma Action Plans

Pankhuri Jha, BS, Jessica F Most, MD

Asthma is a common illness affecting 8% of the US population and costing $81.9 billion per year. Due to its chronic and variable nature, asthmatics need frequent medication adjustments, making management challenging for both physicians and patients. Studies show that patients can control their asthma using an asthma action plan (AAP), which includes directions for daily self-assessment, baseline medications and steps to facilitate detection and treatment of an exacerbation. Self-management education using AAPs is associated with a reduction in hospital admissions and ED visits by 40% and 20%, respectively. Despite evidence that AAPs are efficacious, the underlying reason for their success is not well understood. One hypothesis is that AAP implementation can increase patient confidence in managing asthma; however the literature regarding this topic is limited. Thus, the aim of our study was to determine whether AAP implementation leads to increased patient confidence in managing asthma.

Patients with a physician diagnosis of asthma without a current AAP at the time of their specialist visit were recruited to participate. An eight-question Likert Scale survey developed previously was used to gauge confidence regarding asthma management. At the initial visit, each patient completed the survey and received a personalized AAP along with a peak flow meter. Asthma control was assessed pre and post-AAP implementation using the Asthma Control Test (ACT), a validated measure of asthma control. A score of 19 or greater on the ACT indicates good control. The success of AAP implementation in increasing patient confidence and asthma control was determined by comparing pre and post-survey responses and ACT scores.

We recruited 71 patients, 17 of whom were excluded for lack of follow-up. Of the 54, 25 (46%) had severe, 21 (39%) had moderate and 8 (15%) had mild asthma. The mean patient age was 55.8 years and 63% were females (34/54). Patient confidence using a peak flow meter increased by 45%, with 48% (26/54) rating confidence at ≥ 3 (4 being ‘strongly agree that I am confident’) at the initial visit to 93% (50/54) post-AAP implementation. Fifteen percent more patients felt confident managing asthma symptoms during an exacerbation, with 95% (51/54) rating confidence at ≥ 3. The same 15% increase was observed when gauging patient confidence in knowing personal asthma triggers, with 89% (48/54) rating confidence at ≥ 3. Recognizing asthma symptoms and confidence in preventing asthma symptoms from occurring saw a 4% increase and 9% increase, respectively after AAP education. The mean pre and post-AAP Likert Scale survey scores were 23.28 and 25.70, respectively. AAP implementation was associated with significantly higher mean scores (p=.0001).

ACT data was available for 47/54 (87%) patients. Mean pre and post-AAP ACT scores were 18.49 and 20.11 respectively, and 68% (32/47) of patients scored a ≥ 19 on the follow-up ACT. AAP education was associated with significantly higher mean ACT scores (p=.0043).

There is limited data examining the direct relationship between AAP implementation and patient confidence in managing asthma. Our study is the first that demonstrates AAP administration directly increases patient confidence in managing asthma while improving asthma control. Limitations to our study include the variable time interval for follow-up and the lack of ongoing assessment to account for the variable nature of asthma control.

We found that AAP implementation was beneficial to our patient population in increasing self-reported confidence in asthma management and improving asthma control. With an increasing reliance on telemedicine visits during the COVID-19 pandemic, the importance of self-management has been brought to the forefront. AAPs are a simple and effective tool that permit physicians to hand control over care to their patients and are instrumental in promoting self-management.

REFERENCES


Conflicts of Interest: No conflicts of interest to disclose.
Funding: No funding provided.
Evaluation of Asthma Control in Patients with and without Sinonasal Polyps following Treatment with Biologic Agents

Prachi Patel, BA, Chandala Chitguppi, MD, Alan Gandler, MD, Kira Murphy, MD, Tawfiq Khoury, MD, Stephanie Bork, CRNP, Pamela Monostra, PA, Elina Toskala, MD, PhD, Mindy Rabinowitz, MD, Marc Rosen, MD, Gurston Nyquist, MD, Jessica Most, MD

Conclusions: Patients with and without sinonasal polyps who begin biologic therapy are shown to have significant improvements in their ACT score at follow-up. In addition, patients with polyps are shown to have significantly better control of their asthma while on biologics than patients with no polyps. Comorbid CRSwNP may predict response to biologic therapy in those with severe asthma (SA).

INTRODUCTION

Asthma is a common condition affecting 25 million people in the US including 6 million children. It accounts for nearly 1.8 million emergency room visits per year and 13.8 million missed school days per year. Despite many pharmacologic advances in the past two decades, over 45 percent of asthmatics reported an asthma attack in the past year. Furthermore, 5-20 percent of asthmatics are considered to be refractory despite adequate maintenance inhaled therapy with frequent exacerbations and poor symptom control.

The complex biologic mechanism of airway inflammation associated with asthma has been elucidated over the last 30 years. This has led to a revolution of pharmacologic targets and the recognition of several biomarkers that have allowed for a more personalized approach to asthma. Up to 70% of patients with asthma have evidence of type 2 inflammation, which can be modulated by biologic therapies. These biologic therapies include antibodies against immunoglobin E, interleukin (IL)-5, the IL-5 receptor, IL-13, and IL-4. Unfortunately, many of these therapies have overlapping clinical criteria for use, and to date there is not a standardized approach to choosing biologics.

Many patients with severe asthma (SA) have other comorbid conditions including sinonasal polyps, allergic rhinitis, and chronic idiopathic urticaria. Since some of these biologic agents have been shown to have efficacy in these other disease states, they may serve to identify patients who would benefit from a particular agent. We aim to evaluate whether having sinonasal polyps in severe asthma predicted response to biologic therapy.
METHODOLOGY

Case Selection
All patients with asthma and sinonasal polyposis who underwent therapy with a biologic agent were evaluated in a retrospective manner from 2017 to 2019. A cohort of patients with asthma without sinonasal polyps were also evaluated for comparative analysis. The biologic therapies investigated in this study were omalizumab, mepolizumab, benralizumab, and dupilumab. It is important to note that each of these therapies has a different mechanism of action, but all are approved for patients with severe asthma that is driven by type 2 inflammation. Chart abstraction included asthma control test (ACT) scores, forced expiratory volume at one second (FEV1) pre and post therapy, demographic data, comorbid conditions, fractional exhaled nitric oxide (FENO), absolute eosinophils, respiratory related complications, and progression of symptoms from initial presentation. The ACT is a validated measure for asthma control with a score of >19 considered well-controlled. This along with FEV1 was followed to determine treatment success. Patients with incomplete records, inconsistent data and absence of definitive diagnosis for either asthma or sinonasal polyps were grounds for exclusion.

Statistical Analysis
Patients with a physician diagnosis of asthma, were divided into two subgroups – those with and without sinonasal polyposis on endoscopic examination by an otolaryngologist. Descriptive statistics (mean, median, standard deviation and confidence intervals (CI)) were calculated wherever relevant to summarize overall patient characteristics and outcomes. Statistical t test (compare continuous variables) and Fisher exact test (compare categorical variables) were used to compare asthma control and complication rates between the two subgroups. Further statistical analysis was done to identify patient, polyp and treatment related variables associated with control of asthma on biologics therapy. A two-tailed $P$ value of 0.05 was considered statistically significant and all limits reported are provided for 95% confidence intervals. Institutional review board approval was obtained from Thomas Jefferson University Hospital.

RESULTS

Overall patient characteristics
A total of 82 patients met inclusion criteria with a diagnosis of moderate to severe asthma receiving treatment with an approved biologic agent: omalizumab, mepolizumab, benralizumab, dupilumab. Forty (47.5%) patients from this cohort suffered from concurrent sinonasal polyposis. For patients with asthma without sinonasal polyps (n=42), five were managed with omalizumab, fourteen with mepolizumab, nineteen with benralizumab, and four with dupilumab. Likewise, for patients with concurrent sinonasal polyps, three were managed with omalizumab, ten with mepolizumab, twenty four with benralizumab, and three with dupilumab. Table 1 summarizes the relevant phenotypic variables for each subgroup of patients. Overall, the mean age at time of treatment was 49.65 ± 15.96 years (range 14-81 years) and the mean preoperative body mass index (BMI) was 29.73 ± 6.69 kg/m² with a median BMI of 28.53 kg/m² (range, 16.21-42.40). The majority of the patients were females (64.6%, n=52). In addition, approximately a quarter of the study population were either past or current smokers (25.6%, n=21) while the rest had no history of smoking at the time during treatment. For patients with sinonasal polyps, 95% (n=38) had history of prior nasal surgery.

<table>
<thead>
<tr>
<th>Therapeutic Biologic</th>
<th>Asthma &amp; Sinonasal Polyposis</th>
<th>Asthma Only</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>82</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>50.6 ± 16.3</td>
<td>48.7 ± 16.2</td>
<td>0.59</td>
</tr>
<tr>
<td>Male</td>
<td>52.50%</td>
<td>18.80%</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking Hx</td>
<td>20.00%</td>
<td>31.30%</td>
<td>0.25</td>
</tr>
<tr>
<td>Serum IgE (IU/L)</td>
<td>723.8 ± 275.4</td>
<td>800.6 ± 583.0</td>
<td>0.45</td>
</tr>
<tr>
<td>Absolute eosinophil count</td>
<td>896.3 ± 306.4</td>
<td>563.4 ± 258.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>7.50%</td>
<td>12.00%</td>
<td>0.50</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>25.00%</td>
<td>33.30%</td>
<td>0.41</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>60.00%</td>
<td>45.20%</td>
<td>0.18</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>7.50%</td>
<td>9.50%</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Table 1. Summary of descriptive variables for patients with asthma on biologic therapy

Comparison of pulmonary function in patients with and without sinonasal polyps
Of the 82 patients, 40 (48.8%) had documented sinonasal polyps by an otolaryngologist. Patients with and without sinonasal polyps were found to be comparable in terms of age, pre-treatment BMI, and smoking status. Interestingly, there were significantly more females in the subgroup of patients with asthma without sinonasal polyps. Furthermore, patients with asthma and concurrent sinonasal polyps were found to have significantly higher baseline absolute eosinophil counts, 896.3 ± 306.4 versus 563.4 ± 258.4 in patients without sinonasal polyps. At baseline (time of biologic enrollment), the overall average ACT score for the patients without polyps was 13.16 ± 4.12. At approximately 4 months following initiation of biologic therapy, the overall average ACT score for patients without polyps was 16.45 ± 4.79. As summarized by Table 2, the average ACT scores for patients within each individual biologic subgroup ranged from 11.33 to 17.00. There was an overall 25% percent increase in ACT scores from baseline to long term follow-up, and this was found to be statistically significant
The average ACT score increased to 20.19 + 1.68. ACT scores for individual biologic regimens are further summarized in Table 2. The subgroup of patients without sinonasal polyps had an overall 27.4% increase in ACT scores from baseline to long term follow-up (p<0.001). Patients with polyps had significantly better control of their asthma at baseline than patients with no polyps (p=0.001). However, both groups of patients had poor average baseline asthma control (ACT< 19). Patients with polyps continued to have significantly better control of their asthma at long term follow-up (p <0.001). By 4-7 months patients with polyps were, on average, were able to achieve an overall ACT score of greater than 19 (mean= 20.19), demonstrating the ability to achieve well controlled asthma after initiation of biologic therapy (Figure 1a-d). Furthermore, the subgroup with asthma and concurrent sinonasal polyps had a significantly greater number of total ACT scores greater than 19 at long term follow up than patients without sinonasal polyps (p< 0.05).
When assessing pulmonary function, patients without sinonasal polyps had a baseline average FEV1 of 1.86 + 0.17. Following 4-7 months on biologic therapy, these patients had an increase in average FEV1 to 2.10 + 0.18, representing an improvement in pulmonary function. For patients with sinonasal polyps, the average baseline FEV1 was 1.89 + 0.46, which was found to increase to 2.39 + 0.12 at long term follow-up. Though both groups showed improvement in pulmonary function at 4-7 months, patients with concurrent sinonasal polyps were found to achieve significantly greater improvements from baseline FEV1 when compared to patients without sinonasal polyps (p<0.0001).

**Symptomatology**

Patients presenting to otolaryngology with sinonasal polyps were noted to have multiple symptoms including pain, congestion, headaches, and loss of smell. Of the 40 patients with sinonasal polyps on biologic therapy, 62.5% presented with complaints of anosmia. Following 4-7 months of therapy on a biologic agent, only 15% of the patients continued to present with anosmia. Furthermore, symptoms of pain, congestion, and headaches all decreased on long term follow-up.

**DISCUSSION**

The pathophysiology in severe eosinophilic asthma involves type 2 inflammation characterized by signaling from IL-4, IL-5, and IL-13. Furthermore, patients with chronic rhinosinusitis with sinonasal polyps (CRSwNP), a known type 2 dominant inflammatory process characterized by extensive tissue eosinophilia and increased local IgE, may also benefit from biologic therapy. However, the indications for biologic therapy are imprecise and the ability to predict which biologic will render the best results has proven to be difficult. All of the approved biologic therapies for asthma have been shown to reduce asthma exacerbations and improve symptoms control. For patients with CRSwNP, the efficacy of biologics and their indications are more controversial due to the lack of complete clinical trials. Dupilumab, recently approved by the FDA for treatment of sinonasal polyps, has shown to reduce polyp burden in patients including reduction in polyp size and improved sinonasal symptoms. Clinical trials for omalizumab, mepolizumab, and benralizumab are currently being conducted to provide further information of their efficacy in treating sinonasal polyposis. Whether or not other comorbidities of asthma, including sinonasal polyposis, may help predict success with these medications has yet to be determined.

In our study, patients on biologic therapy with asthma and concurrent sinonasal polyps showed greater symptomatic improvement at long term follow-up, as measured by ACT score (ACT= 20.19 + 1.68), than those without sinonasal polyps (ACT= 16.45 + 4.79). This may be that sinonasal polyps in patients with asthma represent another marker of type 2 inflammation and therefore predict better success with biologic medications. These findings are echoed in a randomized control trial conducted by Bachert et al., where lung function was found to be improved in patients with asthma and CRSwNP despite high or low baseline blood eosinophils. Furthermore, the significant improvements seen in the group with sinonasal polyposis could be due to concomitant improvement in their upper airway disease as suggested by a prior 2006 prospective study that found that an improvement in upper airway disease correlated with an improvement in asthma symptoms. Furthermore, patients with polyps managed on medical therapy were found to have prolonged asthma control when compared to those managed surgically.

The better asthma control found in patients with asthma and sinonasal polyps in our study may also be explained by a tendency for patients to place a greater emphasis on upper airway symptoms versus lower airway as well as an improved ability to breathe through the nose. A prospective study done by Miller et al. proposed that upper airway obstruction may lead to excessive drying of the lower airways due to increased mouth breathing. Improvement of this obstruction may be associated with relief of more subtle lower airway symptoms. Given these findings, determining whether sinonasal polyps independently predict success from biologic therapy in asthma warrants prospective studies.

Currently there is no preferred biologic therapy in severe asthma. In our cohort, dupilumab demonstrated the greatest improvement in asthmatic patients with comorbid polyps, showing improvements from an ACT of 11.50 + 3.53 at baseline to 18.00 + 2.12 on long term follow-up (increase= 56.5%). A randomized control trial completed in 2016 demonstrated that patients treated with dupilumab had improvement in sinonasal imaging scores, sinonasal symptom scores, and sense of smell, thus further emphasizing the effects of dupilumab on CRSwNP. Our study data also found mepolizumab and omalizumab to have greater improvements in polyposis population than benralizumab, for which the least evidence exists in sinonasal polyps. In our study cohort of asthmatics without sinonasal polyps, improvements in ACT were more modest. Aside from omalizumab, none of the others reached a clinically significant improvement of 3 on ACT at long term follow-up. Overall, the number of patients in each group are too small to draw conclusions on the correct biologic with or without sinonasal polyps, though our data reinforces the benefit of each biologic therapy in severe asthma.
The most common presenting symptom in patients with sinonasal polyps was anosmia (62.5%), and after 4–7 months of therapy on a biologic agent, only 15% of the patients had persistent anosmia. A cross-sectional study completed by Vizuete et al. proved that anosmia may be a significant clinical marker for comorbid severe asthma in patients with sinonasal polyposis. Furthermore, because of the frequency and severity of anosmia on a patient’s quality of life and function, it should be an important consideration when determining treatment regimens for patients with sinonasal polyps. Our data shows that biologics may play a role in ameliorating symptoms such as anosmia, and may serve as an additional consideration when deciding to start a severe asthmatic on biologics.

The major limitations of this study is the retrospective study design and small sample size. Additionally, the difference in baseline eosinophils may be a confounding variable in the outcomes. Future studies on the effects of biologics on patients with comorbid sinonasal polyposis should include larger sample sizes with matched controls in a prospective design.

Our study suggests that sinonasal polyps with comorbid asthma may represent a high type 2 high population that may benefit more from biologic therapy. Many patients with sinonasal polyps have concurrent asthma along with the shared immunologic characteristics has led to some to suggest a united airway. Presence of sinonasal polyposis in the setting of severe asthma should warrant consideration of biologic therapy.

CONCLUSION

Patients with and without sinonasal polyps who begin biologic therapy are shown to have significant improvements in their asthma control at follow-up. In addition, patients with polyps are shown to have significantly better control of their asthma while on biologics than patients with no polyps. Thus, comorbid sinonasal polyposis can be considered an additional marker when considering initiation of biologic therapy for severe asthma.

REFERENCES

A Letter to M

Shifa Gandhi, MD

Alone and on call as an intern.
The text came in at 6:45- an admission.
I didn’t even have a chance to sit down and start the mechanical morning routine of chart checking.
I felt slightly comforted in knowing that the pulmonary fellow had already laid eyes on you.
I decided to see you first, and then round on the old folks.
You were asleep when I walked into the ED.
It took a great deal to wake you up.
You looked at me and I saw the distress. The difficulty breathing. It pained me.
I called out “M”. You squeezed my hand in response.
I left your room, slightly uneasy.
Your Parkinson’s was so advanced that you could not clear your secretions. I knew if you got on the vent, you probably were not coming off of it.
I did all I could do to prevent it.
I ran to your room every hour: when your breathing became faster, when you became more confused.
I was the one who had the conversation with your daughter about the potential intubation, that there may be a chance once you were on the vent you would not be able to come off of it.
I remember her tears.
I remember her fear.
I remember that feeling of helplessness because I felt it too.
I left.
The next day you were in the ICU, M.
I couldn’t save you.
In your eyes I saw pain and fear.
I couldn’t heal you.
I’m sorry.
On morning pre-rounds during my Methodist rotation, I was rushing to see all the patients in anticipation of the bolus of admissions that would be coming in soon. I spotted the gray and yellow cart near my patient’s door and opened the cart door while simultaneously trying to fit my handoff into a scrub pocket. I was about to knock on the door with my gown and gloves on, but my flimsy gown was falling so I ended up opening the door with my leg as I was retying it around my neck. The nurse down the hall briefly looked at me and smiled as if I was doing a whimsical dance. “And we don’t knock on doors anymore?” said Mr. W in his resounding voice and skeptical tone. Frozen in the doorway, my hand was still clinging to the doorknob as I straightened my back and offered a sincere apology. No reply from Mr. W except an annoyed gaze as he put his cereal spoon down. I let go of the doorknob and approached him. I asked him how he was feeling now but he looked away and gave no response. “What about your shortness of breath? Is it better now?” I asked. He finally responded, “Just wait until you see me walk down the hallway then you’ll see how short of breath I get.” I asked him if he had gotten a chance to walk the hallways yet and he hadn’t. He then asked me to leave his room and I obeyed.

My initial reaction was feeling a sense of guilt and frustration at not being able to get through to this patient on one hand and resentment towards his behavior on the other. But Mr. W was infamous for being “difficult” as my intern warned me earlier that week, so I took a step back to reassess the situation. His medical record had other instances of negative interactions with providers in the past, the definition of the so-called “difficult” patient. Was it simply a result of his personality, as suggested by an initial glance at the encounter? Perhaps his chronic conditions included a bad temper and angry disposition that led to deflection of any meaningful engagement with providers. Were a few problematic encounters enough for me to impart such a judgement on him, especially knowing they would forever put a label on him during his future visits? The answer was no, of course, and besides Mr. W appeared cheerful when speaking with his family members over the phone.

Mr. W questioned each test, lab, or medication offered to him as to whether it was actually going to help him get better. At one point, he wanted to speak to representatives from patient relations and hospital administration, but even a great amount of explanation couldn’t lessen his skepticism toward medical treatment. What made him “difficult” was not simply a result of his personality but seemed to stem more from his perception of suboptimal, or worse, ill-intentioned treatment. Being an African American male potentially contributed to this perception for historical reasons. Furthermore in Mr. W’s case, he told us he felt dismayed at being discharged before a “full medical recovery” or at least his expectation of such a recovery. He lived with the idea that he could somehow get better enough for his sickness to leave him altogether. Repeated explanations of the pathophysiology of heart failure and lymphedema of the legs could not reassure him. But instead of focusing on Mr. W’s seemingly counterproductive behavior, I decided to use my role as his provider to try to change the pattern of our encounters.

In part, what had made me perceive Mr. W as a “difficult” patient had to do with my own experience with patients who would not open up to me for help on their own accord. My first reaction of feeling frustrated at not being able to talk to him meant that it was actually the conversation that was the difficult part. I had to find a way to have a meaningful conversation, so I thought back to the time in medical school when I was taught to begin medical interviews with an open-ended question followed by a period of reflective listening. This is where I would reiterate back to the patients their narratives in my own words in order to make them feel heard. Another strategy would be to reflect the feelings they were conveying through their narrative or body language if they decided to keep silent. Although it seemed archaic when I learned it as a student, I now felt it was a tool I could use to help this patient, so I decided to give it a try.

I was once again met with silence when I entered his room. “It must be really hard having to live like this,” I said as I approached him. “You have no idea,” he replied with a weak smile for the first time. He had a look of helplessness and shame on his face and was starting to cover himself with a blanket. Living with huge legs was not easy and he deserved some empathy. Finally, after days of refusing to be discharged from the hospital, he came around to it. I brought a computer to his room and showed him his lab results and follow-up appointments per his request. He let me explain to him the importance of taking his medications and keeping his appointments. As I was leaving the room, he thanked me but also said that he was planning to come back to the hospital next week in his usual sarcastic tone. This time, however, he seemed to be in good spirits and even sounded friendly. “You’re welcome to if needed” I said, “and we’ll take good care of you each time.” He was still smiling as I left the room.