# The Medicine Forum

The Journal of Thomas Jefferson University Hospital Department of Internal Medicine, Volume 21, 2019 – 2020





HOME OF SIDNEY KIMMEL MEDICAL COLLEGE

## FROM THE DESK OF THE RESIDENCY PROGRAM DIRECTOR



#### To Friends of the Department of Medicine

It has been a historic year for the Nation, City of Philadelphia and the Jefferson Internal Medicine Residency Program. We have experienced many health care crises starting with the closure of the historic Philadelphia hospital, Hahnemann. We welcomed residents from this program as part of the Jefferson Family and integrated many patients into our practices. This was followed by the first pandemic in over a century. Through all of this as the Program Director, I have never been prouder of our residents. They have risen to every challenge with grace and poise working alongside faculty to support the Jefferson mission: We Improve Lives. This mission has never been more important as people across the country protest the institutional racism that plagues this country. In the midst of all of this the 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.

This journal, now in its 21th 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

## FROM THE **EDITORS**

#### Dear Students, Residents, Faculty, and Friends of the Forum,

We are delighted to present you with the 21st annual edition of *The Medicine Forum*. Here in the birthplace of our nation, we like to think of *The Medicine Forum* as being of the housestaff, by the housestaff and for the housestaff. Undeniably, this publication would not be possible without the countless hours dedicated by our residents, students, fellows and faculty.

This year has not been normal. The international healthcare community has been confronted by a pandemic that has posed challenges unlike anything seen by our generation. Our residents and faculty have been at the frontline of treating and better understanding Covid-19. While we eagerly await the results of multiple clinical trials that will continue to shape our management of this disease, we are also excited to share other areas of ongoing scholarship within our department.

As always, thank you for reading The Medicine Forum. We hope you will continue to support us in the years to come.

Sincerely,

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REFUSING TO BE LABELED	
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### CLINICAL IMAGES

## Bilateral Intercostal Lung Herniations: A Rare Incidental Finding in a Dyspneic Patient

Jillian Cooper, MD and Christine Kurian, MD

#### **CASE PRESENTATION**

A 63-year-old man with a past medical history of chronic obstructive pulmonary disease (COPD), stage IV sarcoidosis on 3-4 liters of home oxygen and chronic prednisone, moderate aortic stenosis, and a prior aspergilloma for which he had a left upper lobe lung resection presented to the hospital with two weeks of worsening shortness of breath. His symptoms were thought to be multifactorial secondary to community-acquired pneumonia, sarcoidosis flare, and pulmonary edema. He was treated with an increased dose of steroids, antibiotics, and diuretics with symptomatic improvement. He was discharged on 40mg prednisone daily with a plan to taper as an outpatient.

Notably, CT scan on admission showed under-aerated lung parenchyma via chest wall defects, consistent with bilateral intercostal lung herniations **[Figure 1]**. He had known longstanding right-sided lung herniation, and in 2010, it was documented that he had recent development of left-sided herniation as well. These were attributed to frequent coughing spells related to his sarcoidosis. He was evaluated by thoracic surgery, and due to his overall poor lung function, surgical intervention was thought to be of little potential benefit. Additionally, given his history of aspergillus, surgical repair was thought to be a higher risk procedure than usual, as repair often involves placement of a foreign body (mesh). Lastly, he did not have much discomfort from the hernias, and thus it was thought that there was a greater risk from intervention rather than benefit.

#### DISCUSSION

A lung hernia is an out-pouching of pulmonary parenchyma through a defect in the chest wall. Lung herniations can be classified based on etiology and anatomical location (thoracic and cervical). Intercostal herniations are classified as congenital (18%), acquired-traumatic (52%), or acquired-spontaneous (30%).<sup>1,2</sup> These can develop due to increased intrathoracic pressure with concurrent weaknesses in the chest wall.<sup>3</sup> Symptoms include pain with inhalation, coughing, or sneezing; shortness of breath; soreness; or swelling. Long-term complications of lung hernias include recurrent pulmonary infections and strangulation.<sup>2</sup> Few cases of bilateral thoracic lung herniations are documented in the literature.<sup>4</sup> Repair is often indicated in cases with pain and entrapped lung.



Figure 1: Chronic lung changes of end-stage sarcoidosis with right mid-lung abnormality corresponding to under-aerated right middle lobe lung parenchyma via chest wall defect, also seen on left, secondary to chronic intercostal herniation of lung.

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## An Approach to Refractory Hypoxemia

Daniel Garrido, MD, Evan Nardone, MD, Mark Mallozzi, MD

#### INTRODUCTION

Oxygenation normally occurs through a process of passive diffusion through the pulmonary capillaries, where oxygen binds to hemoglobin or plasma. When the oxygenation is deemed insufficient, a decrease in the partial pressure develops, resulting in hypoxemia. This is in contrast to hypoxia, which develops when there is a low presence of oxygen at the level of the tissue.<sup>1,2</sup> The oxygenation of hemoglobin is most often measured through the arterial oxygen saturation (SaO2), which represents the proportion of hemoglobin that is bound to oxygen in red blood cells. This is represented most commonly through pulse oximetry, which is normally >95% in healthy adults.<sup>3</sup> To accurately measure the amount of oxygen dissolved in plasma, the arterial oxygen tension (PaO2) is measured, which is represented through an arterial blood gas (ABG).

One method to measure oxygenation is through the calculation of the A-a oxygen gradient. This measure identifies the difference between oxygenation within the alveoli (PAO2), and within that dissolved in plasma (PaO2). This gradient represents how well gas is exchanged between the alveolar and capillary membranes. When the difference in the A-a gradient (PAO2-PaO2) is normal (<10mmHg), etiologies for respiratory failure are typically from alveolar hypoventilation or low inspired FiO2. However, when there is a widened A-a gradient, etiologies may include ventilation-perfusion (V/Q) mismatch, right-to-left shunting, or a diffusion defect.<sup>4</sup> When in the presence of oxygen there is no improvement in a patient's hypoxemia, then the hypoxemia is deemed refractory. Herein we present an unusual case of refractory hypoxemia in a patient with patent foramen ovale (PFO) and extensive deep vein thromboses (DVT).

#### **CASE DESCRIPTION**

A 74-year-old female with no significant pulmonary history presented as a transfer from an outside hospital for persistent refractory hypoxemia. ABG on admission was noted to be pH 7.50, pCO2 25, pO2 58, and HCO3 of 20 while on 13L nasal cannula. She was noted to have an A-a gradient >400. The patient was also noted to desaturate to 70-80% O2 saturation with movement and when sitting up (suggestive of orthodeoxia-platypnea syndrome), which continued despite being transitioned to high-flow nasal cannula and intermittent BiPAP therapy. Extensive workup had been performed for her hypoxemia including chest CTA, methemoglobin levels, and autoimmune serologies, which were negative. However, ABG persistently demonstrated 30% shunt fraction. Transthoracic echocardiogram (TTE) with bubble study was concerning for a PFO. Subsequent transesophageal echocardiogram (TEE) confirmed an ascending aortic aneurysm forcing the PFO open with large and rapid right-to-left shunting. After presuming a right-to-left shunt as the primary cause of hypoxemia, a right heart catheterization (RHC) was performed with an attempted PFO closure (as the patient was not a surgical candidate). RHC demonstrated pulmonary arterial (PA) pressures of 25mmHg/10mmHg. During the procedure a left atrial clot was incidentally found and cleared with catheter removal. However, intra-procedural closure of the PFO resulted in hypotension and no improvement in oxygenation. Given the left atrial clot and the discovery of bilateral lower extremity DVT on ultrasound, a lung perfusion scan was performed to evaluate for chronic thromboembolic disease (as the patient could not tolerate a ventilation scan), however the result was normal. It was ultimately believed that her poor oxygenation was due to her PFO with frequent changes in the shunt due to position and hemodynamics. After a goals of care discussion, the patient was transitioned to comfort care and discharged on hospice.

#### DISCUSSION

We believe this case provides a good opportunity to work through a differential for refractory hypoxemia. Despite extensive testing, the ultimate etiology of the presented patient's hypoxemia was unclear at the time of her discharge to hospice. Below we discuss the typical differential for hypoxemia and apply it to the case above.

1. Right-to-left shunt: During right-to-left shunting, hypoxemia is caused by deoxygenated blood mixing with oxygenated blood in the systemic circulation. This can be from anatomic defects such as intracardiac shunts (PFO, VSD, etc.), pulmonary AVMs, or processes causing intrapulmonary vasodilation (i.e. hepatopulmonary syndrome). Shunting can also be physiologic during which non-ventilated lung are perfused which can occur in pneumonia, ARDS, atelectasis, etc. Typically, these patients have hypoxemia, which is difficult to correct with supplemental oxygen. Our patient had an appropriate workup for intracardiac shunting and ultimately a PFO was found on TEE. Furthermore, it was thought that her ascending aortic aneurysm was forcing her PFO open in certain positions causing her to have positional desaturations. Interestingly, however, when her PFO was occluded during cardiac catheterization, her oxygenation did not improve and ultimately closure was aborted due to hypotension. It is unclear why her oxygenation did not improve with occlusion of her shunt.

- 2. V-Q mismatch: Some degree of perfusion and ventilation mismatch occurs physiologically in the healthy lung but is worsened in the diseased lung state. Hypoxemia can occur by this mechanism when there is a decrease in the ventilation or perfusion of a lung segment impairing oxygenation of blood. In our patient, given her extensive clot burden with left atrial clot and bilateral lower extremity DVTs, it was thought that pulmonary emboli may have been causing defects in perfusion to her lung and contributing to her hypoxemia. She was unfortunately unable to tolerate a ventilation scan but had a perfusion scan that was normal, making this etiology less likely.
- 3. Diffusion limitation: Hypoxemia by this mechanism occurs when there is a diminished ability for oxygen to diffuse from the alveolus to the capillary. It is commonly due to interstitial lung disease causing interstitial inflammation and fibrosis. Our patient did not have findings on her chest imaging that were indicative of interstitial inflammation. Additionally, she had an extensive autoimmune serologic workup that was negative. Hypoxemia by this mechanism is commonly worsened by exertion and improved with rest. Our patient had profound hypoxemia at rest making this etiology less likely.
- 4. Hypoventilation: During hypoventilation, both arterial and alveolar CO2 increases which causes decrease in alveolar oxygen tension. Hypoxemia due solely to hypoventilation will have a normal A-a gradient, will have primarily elevated PaCO2, and will rapidly correct with increased FiO2. A typical presentation may be a patient with obesity hypoventilation, disorders causing respiratory muscle weakness, or CNS depression. Our patient did not have evidence of hypoventilation on her blood gas making this etiology for hypoxemia less likely.
- 5. Decreased fraction of inspired oxygen (FiO2): This causes hypoxemia by decreasing the oxygen gradient from the alveolus to the artery. This is typically associated with high altitudes and not a likely etiology for our patient given her history.

Ultimately, it was decided that the most likely etiology of our patient's hypoxemia was due to right-to-left intracardiac shunting, but it remains unclear why her hypoxemia did not improve with PFO occlusion during cardiac catheterization. Given her substantial lower extremity clot burden and the presence of intracardiac blood clots, it is possible that V/Q mismatch was also contributing to this patient's hypoxemia with intrapulmonary shunting. However, her right-sided and pulmonary pressures on TTE and RHC did not show evidence of pulmonary hypertension that would be expected in V/Q mismatch due to chronic thromboembolic disease. Although less likely, we cannot rule out this as a contributing factor to her hypoxemia since she was not able to tolerate a full V/Q scan. This case highlights an atypical presentation with multiple possible etiologies of hypoxemia and provides an opportunity to work through a broad differential for this problem.

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## Pericardial Effusion with Tamponade Physiology in a Patient with Multiple Myeloma

Sairamya Bodempudi MD, Rukaiya Bashir Hamidu MD, Preya Simlote MD, Shuwen Lin MD, Philip Margiotta MD, Tina Boortalary MD, Gregary D. Marhefka MD



**Figure 1.** (A) RA diastolic collapse showing evidence of early tamponade. (B) Plethoric IVC from a subcostal view. (C) Circumferential shot from a subcostal view to show the extent of the pericardial effusion.

#### **INTRODUCTION**

Both solid and hematological malignancies are known to cause pericardial effusions. The hematological malignancies that most often cause pericardial effusion are leukemias, Non-Hodgkin's lymphomas, and Hodgkin's lymphomas.<sup>1</sup> Patients can also develop pericardial effusions from cancer-related causes, such as chemotherapy, immunotherapy, radiation, or infection.<sup>2</sup> Although it has been reported in the literature (approximately 27 cases between 1970 to 2019), malignant pericardial effusion from multiple myeloma is relatively uncommon.<sup>3,4</sup> In addition, a rare but known complication of poorly controlled multiple myeloma is hyperviscosity syndrome, which typically presents as spontaneous hemorrhage of the mucosal membranes, headaches or neurological symptoms. We present a case of a patient with multiple myeloma who was found to have a pericardial effusion with tamponade that was also complicated by hyperviscosity syndrome.

#### **CASE PRESENTATION**

#### **History of Present Illness**

A 78-year old African American female with a past medical history of IgA Kappa Multiple Myeloma was transferred to the Cardiovascular Intensive Care Unit (CVICU) at Thomas Jefferson University Hospital (TJUH) after being diagnosed with a pericardial effusion with tamponade physiology at an outside hospital.

The patient was diagnosed with multiple myeloma 3 years prior on a left maxillary biopsy revealing a plasmacytoma. Due to medical complications, multiple hospitalizations, poor follow up, and intermittent refusal of chemotherapy, the patient never achieved remission of her malignancy. Due to continued progression of her disease, she was started on Melphalan /methylpred-nisolone therapy and had finished 5 cycles.

The patient was in her usual state of health until one week prior to presentation when she developed a cough and dyspnea on exertion. Since her symptoms progressed, she eventually went to the emergency department, where she was noted to have a pericardial effusion with signs of early tamponade physiology. She was transferred to the CVICU at TJUH for further care.

Upon arrival to TJUH, the patient was tachycardic with heart rates in the 110s. A physical exam revealed jugular venous distension, normal S1 and S2 heart sounds, slight end expiratory wheezing throughout the lung fields, and a droopy right eyelid with nodules. A pulsus paradoxus was found to be 5 mm Hg and a bedside transthoracic echocardiogram (TTE) showed a circumferential pericardial effusion with a maximum size of 2.2 cm, brief right atrial diastolic collapse, and a non-compressible inferior vena cava concerning for early tamponade physiology.

#### **Hospital Course**

Due to concern for tamponade, the patient received a pericardiocentesis with pericardial drain placement. Approximately 185 mL of sanguineous fluid was drained and sent to the lab for typical studies, including cytology plus flow cytometry. A repeat TTE showed trivial residual pericardial effusion with improved hemodynamic profile and resolution of tamponade. Pericardial fluid cytology and flow cytometry results showed evidence of plasma cells consistent with her underlying plasma cell myeloma.

Within a day of admission, the patient developed significant interval swelling of her right eye with ecchymosis of her medial upper eyelid and significant conjunctival hemorrhage. Due to subjective shortness of breath, a chest radiograph was done and showed the correct positioning of the pericardial drain. However, it incidentally showed new left sided pleural effusion. Given multiple sites of spontaneous hemorrhage and significantly elevated IgA levels (>4500), there was concern for hyperviscosity syndrome. Medical oncology was consulted and recommended urgent plasmapheresis, however, the patient initially refused conveying her wishes to pursue non-aggressive medical therapy. She was temporized with intravenous fluids and high-dose steroids.

On day 7 of post-pericardial drain placement, there continued to be high output (>75mL/day) from the drain. Given the increased risk of infection with prolonged drain placement and continued high output in the setting of hyperviscosity syndrome, the decision was made for doxycycline sclerotherapy to the pericardium with subsequent removal of the pericardial drain. Repeat TTE the following day showed only trivial pericardial effusion.

Eventually, the patient consented to plasmapheresis, resulting in a downtrend of her IgA level. She received cytoreductive chemotherapy with cyclophosphamide and dexamethasone. The patient's post-chemotherapy hospital course was complicated by paroxysmal supraventricular tachycardia, acute kidney injury, stressinduced hyperglycemia requiring insulin therapy and febrile neutropenia from an unknown infectious source. These complications resolved with medical management.

Prior to discharge, goals of care were readdressed. Although initially hesitant, the patient and her family ultimately decided to pursue aggressive treatment of her multiple myeloma. She was subsequently discharged to a sub-acute rehabilitation center after which she underwent chemotherapy with daratumumab, pomalidomide, and dexamethasone. Two months after the patient's initial presentation to the TJUH CVICU, the patient is doing well on her current chemotherapy regimen with down trending IgA levels. She has stable pleural effusions on chest x-ray. Repeat TTE's show no evidence of pericardial effusion. She remains symptom free with no further medical complications.

#### **DISCUSSION & CONCLUSIONS**

As stated previously, pericardial effusions secondary to multiple myeloma are very rare, seen in < 1% of cases.<sup>4</sup> Although in our case, the pericardial fluid was determined to be malignant in origin based on flow cytometry and cytology, the rapid re-accumulation of pericardial effusion almost a week after drain placement was presumed to be due to the spontaneous bleeding complications of hyperviscosity syndrome. The medical interventions were unique for this particular patient due to her preference of treatments. She was initially temporized with fluids and dexamethasone instead of immediately being started on plasmapheresis. Interestingly, temporizing measures did initially slow the rate of drain output.

Despite stabilizing with steroids and fluids, the patient's re-accumulating pericardial effusion necessitated management with sclerotherapy. Per review of literature, doxycycline sclerotherapy for recurrent pericardial effusions secondary to multiple myeloma has not been performed.<sup>4</sup> The decision to attempt bedside doxycycline sclerotherapy highlights the role of shared-decision making between the patient, her family, cardiology, medical oncology, and thoracic surgery in order to respect the patient's wishes to opt for minimally invasive treatment strategies.

Our case also explores the complicated relationship between management of plasma cell pericardial effusions and hyperviscosity syndrome, which may increase the risk of bleeding into the pericardium. When the patient is clinically and hemodynamically stable, and willing to receive plasmaphoresis, it is reasonable to treat the hyperviscosity syndrome prior to draining the pericardium to decrease the risk of post-intervention bleeding. However, when a patient presents with early signs of tamponade physiology or hemodynamic instability, then a pericardiocentesis could be considered and prioritized with simultaneous temporization of hyperviscosity syndrome utilizing high-dose steroids and fluids as we had done in this case. Finally, the case demonstrates that it is essential to intermittently revisit goals of care because our patient's wishes evolved and molded her medical management. On-going discussions resulted in her changing her initial decision, and altering the course of her disease process. Our case of a patient with multiple myeloma presenting with malignant pericardial effusion as an extra-medullary manifestation of chemotherapy-refractory multiple myeloma is therefore unique from a clinical presentation, medical intervention, and a shared decision-making standpoint.

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## **Diagnosing Non-HFE Hereditary Hemochromatosis**

Brian Park, MD, Naman Upadhyay, MD, Dina Halegoua-Demarzio, MD

#### ABSTRACT

Non-HFE hemochromatosis is a rare cause of end stage liver dysfunction that is characterized by excessive iron deposition in the liver. The vast majority of primary iron overload is due to well documented mutations of the *HFE* genetic locus, however, rare genetic cases not involving the *HFE* locus have been documented. Here we present the case of a 63-year-old female who developed liver failure due to non-*HFE* hemochromatosis. Secondary causes of iron overload were ruled out, and genetic testing was negative for primary *HFE* (C282Y and H63D) mutations. We discuss the clinical work up involved in making the diagnosis of non-*HFE* hemochromatosis and the treatment options.

**Keywords:** Non-*HFE* Hemochromatosis, primary hemochromatosis, iron overload, hereditary hemochromatosis

#### **INTRODUCTION**

Hereditary Hemochromatosis (HH) is a disease characterized by increased intestinal absorption of iron and subsequent deposition in tissues. Hemochromatosis is a progressive disease that without therapeutic intervention can lead to iron accumulation in tissues leading to organ damage such as liver cirrhosis, diabetes, skin discoloration, and cardiomyopathy<sup>1</sup>.

Primary hemochromatosis due to the *HFE* gene is the most common identified genetic disorder in Caucasians of northern European descent with a prevalence of 1 in 200 individuals and accounting for 60-95% of European iron overload cases<sup>2</sup>. In contrast, most cases of iron overload that do not involve the *HFE* gene are due to secondary hemosiderosis. However, there are rarely observed gene mutations that result in primary hemochromatosis collectively called non-*HFE* hemochromatosis<sup>3</sup>.

#### **CASE REPORT**

A 63-year-old Caucasian female presented for evaluation of abnormal bile duct appearance on ERCP after being diagnosed with gallstone pancreatitis, duodenal ulcers and gastritis at another hospital. Over the past several years she had noticed increasing fatigue, unintentional weight gain of 30 pounds, lower extremity and abdominal swelling. The patient recalls having jaundice at the age of 14, and at age 28 she was told she had hepatitis although her hepatitis testing was negative. She has a history of psoriasis and vitiligo. Her family history is notable for liver disease of unknown etiology in her grandmother, gallbladder and thyroid disease in her mother, daughter with psoriasis, and son with type 1 diabetes mellitus.

She rarely drinks alcohol. She has taken an occasional Aleve for arthritic pains but had not taken any NSAIDs in two years. She does not smoke cigarettes or use illicit drugs. She worked at a large wholesale grocery as a door greeter.

Her physical exam was notable for prominent scleral icterus, diffuse jaundice, abdominal distension with dullness in flanks but no tenderness, 3+ pitting edema in bilateral lower extremities, chronic vitiligo of hands and chest, palmar erythema, asterixis with mild confusion, but no spider angiomas or malar rash.

Her labs were significant for iron overload with iron saturation of 95%, elevated ferritin of 4400 ng/mL, decreased transferrin to 138 mcg/dL, and iron level elevated to 185 mcg/dL. She had a macrocytic anemia with hemoglobin of 9.0 g/dL, MCV 108 and normal B12 and folate.

Labs were negative for CMV, EBV, VZV, HAVAb, HBGAg, HBVAb, HCVAb, and HIV. Normal AFP (3.7 ng.mL), A1AT (14 mg/dL), TSH (3.4 uIU/mL), A1c 4.1, and low normal ceruloplasmin (19mg/dL). Presenting MELD-Na score was 17 (Cr 0.6, Bili 4.9, INR 1.5, Na 140).

Elevated IgG, but negative ANA and ASMA (ruling out AIH and PBC). Gene mutations for primary *HFE* (C282Y and H63D) were negative.

MRI (Figure 1) was consistent with primary hemochromatosis effecting the non-reticuloendothelial system (non-RES); involving the liver, but not the spleen or bone marrow. Additionally, on the dual-sequence MRI (Figure 2) there is a drop in signal intensity on the image with the longer echo time<sup>10</sup>.

Liver biopsy (Figure 3) demonstrated bridging fibrosis and focal nodularity, stage 3-4. Features of chronic hepatitis evidenced by mild lobular and portal inflammation. Iron stain showing 4+ hepatocellular iron deposit. No evidence of steatohepatitis. No evidence of portal edema or brisk ductular reaction to support biliary obstruction.

Despite treatment her condition progressed to ESLD and she was listed with successful liver transplantation.



Figure 1: Figure 1: T2 weighted MRI showing decreased enhancement of the liver (darker appearance) but not the spleen, characteristic in iron overload due to primary hemochromatosis.

#### DISCUSSION

Hereditary Hemochromatosis (HH) is a disease of iron overload that is most commonly due to mutations of the *HFE* gene. The *HFE* gene mutation most commonly involves a tyrosine for cysteine substitution at amino acid position 282, or protein product C282Y<sup>1</sup>. The allele frequency of C282Y is close to 5% in European populations according to the 1000 Genomes Project and explains the large number of European persons with primary hemochromatosis who are homozygous for C282Y *HFE* gene<sup>2</sup>.

Rarely, there are cases of iron overload consistent with primary hemochromatosis that do not involve the HFE gene collectively called non-HFE hemochromatosis<sup>3</sup>. These non-*HFE* genes include hemojuvelin (*HJV*), hepcidin (HAMP), transferrin receptor (TFR2) and ferroportin (SLC40A1). Though most known forms of primary hemochromatosis have recessive inheritance, SLC40A1 is recognized as a rare autosomal dominant inherited genotype that can be associated with a splicing mutation4. These gene mutations have phenotypes that range from the severe juvenile forms of iron overload as in mutations of HJV and HAMP to the milder phenotypes associated with TFR2 and SLC40A15. Typically, the earlier onset forms involve severe endocrine and cardiac manifestations that can result in death by the age of 30<sup>5</sup>. Notably, ferroportin mutations were first described in 1999 in individuals of Italian and Dutch descent, but were later observed in gene sequencing of Asian, American and African populations<sup>6,7</sup>.

The diagnosis of non-*HFE* hemochromatosis involves ruling out secondary causes of iron overload, quantifying liver iron stores via MRI or liver biopsy, determine the hereditary nature of the iron overload by genetic testing (typically for *HFE* only)<sup>8</sup>. As mentioned previously, MRI



Figure 2: Dual sequence MRI "In Phase and Out of Phase" showing decreased signal of the liver on the "In Phase" image (left) compared to "Out of phase" image (right) which is consistent with hemochromatosis. The iron deposition is more severe in the liver.



**Figure 3:** Iron stain from our patient showing 4+ hepatocellular iron deposition (left blue stain). H&E stain demonstrated bridging fibrosis and focal nodularity, stage 3-4 (right pink stain) Features of chronic hepatitis evidenced by mild lobular and portal inflammation.

did not show involvement of spleen or bone marrow whereas for hemosiderosis or secondary hemochromatosis, iron deposition would be prominent in these locations.

Estimates of the prevalence of non-*HFE* hemochromatosis were previously about 10%<sup>6</sup>. To date, 55 *HJV* cases, 13 *HAMP* cases, 49 *TFR2* cases, and 60 cases of *SLC40A1* disease have been reported?. Next-generation sequencing supports the rarity of these non-*HFE* pathogenic alleles with predicted frequencies ranging from 0.00007 to 0.0004. Compare this to the 5% allele frequency of the C282Y missense substitution as previously noted. Corresponding predicted frequencies of the genotypes range from 1 in 556 for *SLC40A1* to 1 in 6,000,000 for *TFR2* and as rare as 1 in 181,000,000 for *HAMP*<sup>7</sup>.

Heterozygous mutations in SLC40A1 lead to ferroportin disease and we were surprised to find relatively high frequencies of SLC40A1 variants classified as pathogenic. These variants were found at the highest frequencies among African populations (0.25%) but were also present in the American (0.039%), East Asian (0.033%), and non-Finnish European (0.03%) populations<sup>7</sup>. Non-*HFE* HH seems to be more prevalent in southern Europe compared with northern Europe.

Due to the lack of widely available direct gene sequencing, these non-*HFE* genes are not recommended to be tested unless investigating severe refractory cases<sup>8</sup>.

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## An Unusual Treatment for Chronic Myelomonocytic Leukemia

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#### ABSTRACT

Chronic myelomonocytic leukemia is a rare, aggressive, chronic leukemia that frequently progresses to acute myeloid leukemia. For younger patients, treatment ideally involves bone marrow transplant, and, if not a candidate, hydroxyurea or hypomethylating agents are the standard of care for symptomatic patients. Here, we present an unusual treatment of a patient with chronic myelomonocytic leukemia (CMML) characterized by atypical mutations in IDH2 and NPM-1 using Venetoclax and a hypomethylating agent with complete response.

#### **INTRODUCTION**

Chronic myelomonocytic leukemia has features of both myelodysplastic syndrome and myeloproliferative neoplasms. Characterized by an increase in circulating monocytes, the disease frequently progresses to acute myeloid leukemia (AML) and is the most aggressive chronic leukemia. Clonal cytogenetic abnormalities are found in approximately 30% of patients, most commonly trisomy 8, trisomy 21, monosomy 7 and del7q, and other complex karyotypes.<sup>1</sup> For younger, fit patients, treatment ideally involves bone marrow transplant. If not a candidate, cytoreductive strategies using hydroxyurea or hypomethylating agents (HMA) are the standard of care for symptomatic patients. Because of the rarity of this disease, advancement of treatment strategies outside of transplant have been few.<sup>2</sup> This case is presented to demonstrate an unusual treatment for CMML with IDH2 mutation using Venetoclax and an HMA.

#### **CASE PRESENTATION**

A 76-year-old female with a past medical history of an extraosseous chondrosarcoma status-post resection thirty years prior, hypertension, hyperlipidemia, and hypothyroidism presented to her primary care physician with fatigue, two weeks of dyspnea on exertion, lightheadedness, and nausea. The patient's primary care physician ordered a complete blood count, which was significant for a hemoglobin of 6.8 g/dl and she was instructed to go to the Emergency Room for workup. In the ER, the patient was afebrile, and her vital signs were all within normal limits. On exam, she was noted to have a 3/6 systolic ejection murmur. Her lungs were clear to auscultation bilaterally and she did not have any skin abnormalities. She was given a transfusion of packed red

blood cells and her hemoglobin responded appropriately. However, she was found to have thrombocytopenia and a leukocytosis with an absolute monocyte count of 5800 cells/uL (16% of the differential), a total white blood cell count of 36,400 cells/uL, a platelet count of 52,000 per/uL and no eosinophilia.

After being discharged, the patient was seen by oncology and underwent a bone marrow biopsy. Pathology showed hypercellular marrow (95%) with trilineage proliferation, 10% monocytes and 5-10% blasts with less than 10% dysplasia. Flow cytometry, cytogenetics and Next-Generation Sequencing were unable to be performed due to an inadequate sample. Peripheral blood was then analyzed which showed 16% monocytes, 7% blasts and flow cytometry positive for CD4, CD11c, CD13, CD33, CD34, CD38, CD64, HLA-DR and CD117. Cytogenetics showed a normal female karyotype and was negative for BCR/ABL rearrangement. Mutational analysis was positive for IDH2, DNMT3A and NPM1 and was negative for JAK2, CALR and MPL. She was subsequently diagnosed with CMML, given her monocytic predominance and flow cytometry. Due to her excellent functional status (ECOG score of 1), curative treatment with cytoreductive agents and bone marrow transplant was pursued. Because of her NPM-1 and IDH2 mutation, it was decided that a regimen consisting of Decitabine and Venetoclax was appropriate. She began treatment in early February 2019 and, after two cycles, a biopsy was repeated, which showed only 9% abnormal myelocytes and no blasts. The regimen was well-tolerated by the patient and by June she was in complete response (CR) with no complications from treatment. She underwent another biopsy prior to transplant which showed hypocellular marrow with less than 1% monocytes and blasts. She then underwent non-myeloablative bone marrow transplant in November and, as of last follow-up 112 days later, is in recovery. Bone marrow biopsy post-transplant showed normocellular marrow with no increase in abnormal monocytes.

#### DISCUSSION

Chronic myelomonocytic leukemia is diagnosed based on a peripheral monocyte count above 10%, in addition to bone marrow dysplasia. It frequently progresses to an acute leukemia in up to 20% of cases.<sup>3</sup> The median age at onset is during the early seventh decade of life, and it has a slight male preference. There are several classification systems including the World Health Organization classification and the Mayo prognostic model, however the most commonly used is the CMML-specific prognostic scoring system (CPSS). The CPSS classifies patients into various risk categories using their CMML FAB type, cytogenetics, red blood cell transfusion dependence and, WHO subtyping based on the percentage of blasts in the periphery and bone marrow. For low risk patients the median survival is 6 years, for high risk patients it is just 5 months.<sup>1</sup>

The most common mutations in CMML have differing mechanisms, including epigenetic control of methylation (TET2 60%), chromatin modulating (ASXL1 40%), cell signaling pathways (RAS pathway 30%) and mRNA splicing (SRSF2 50%). ASXL1 has been shown to correlate with survival. Mutations in IDH1 or IDH2 are uncommon in CMML, occurring in less than 5% of patients.<sup>4</sup> Although rare in CMML, approximately 15% of patients with AML have a mutation in IDH. Normally IDH is involved in the citric acid cycle and metabolizes isocitrate to 5-alphaketoglutarate. When IDH is mutated, it gives rise to a new metabolic product: 2-hydroxyglutarate (2-HG). 2-HG accumulates and inhibits other enzymes including TET2 and JMJC, both epigenetic modifiers that can lead to leukemogenesis.<sup>5</sup> Cells following this pathway become dependent on the anti-apoptotic gene Bcl-2 for survival.<sup>6</sup>

Due to its association with epigenetic dysregulation, the standard of care for CMML is a hypomethylating agent, specifically azacitidine or decitabine. These medications work by demethylating and subsequently allowing expression of hypermethylated tumor suppressor genes.<sup>7</sup> Unfortunately, only 50% of patients respond to these agents, with less than 20% achieving complete response to these agents alone.1 HMAs are also frequently used in patients with AML who are not candidates for standard chemotherapy induction. Unfortunately, response rates in most studies of patients with AML show a complete response in only approximately 20%.8 In more recent studies, patients over the age of 65 with AML were given the Bcl-2 inhibitor Venetoclax in addition to an HMA. Twenty-four percent of these patients achieved CR, with an additional 43% achieving CR with incomplete cell count recovery.9 To our knowledge, there have been no studies using HMAs plus Venetoclax in patients with CMML, however, Venetoclax has been shown to have efficacy in CLL, AML, and ALL, particularly in patients with IDH mutations.<sup>10</sup> Although this is a relatively rare mutation in CMML, further study of this treatment regimen is warranted in patients who express IDH mutations in CMML and other MDS/MPNs.

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## A Case Report of Hemophagocytic Lymphohistiocytosis Secondary to Disseminated Tuberculosis

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#### **INTRODUCTION**

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder characterized by excessive activation of the immune system causing tissue damage and organ dysfunction. Secondary HLH is more common in adults and is usually triggered by infection, malignancy, rheumatologic, and immunodeficiency syndromes. We present a case of HLH secondary to disseminated tuberculosis (TB).

#### **CASE PRESENTATION**

A 72-year-old woman with past medical history of hypertension and type 2 diabetes presented to the emergency department for one day history of fevers, poor oral intake, and fatigue. She was febrile to 102.9 F and noted to have a toxic appearance, but there were no focal abnormalities found on exam. Initial blood work was notable for a mild direct hyperbilirubinemia of 2.5mg/dL, AST/ALT of 162/112 IU/L and elevated INR of 1.4. Abdominal ultrasound showed gallbladder wall thickening. Due to concerns for ascending cholangitis, ERCP was performed and revealed a normal biliary system. Day 2 of hospitalization revealed new pancytopenia - her white blood cell count was 2.7 B/L with 44% bands, hemoglobin was 10.8 g/dL, and platelet count was 39 B/L. She also had rising hepatic function tests. Her ferritin on day 3 was significantly elevated at 4149 IU/L, raising concerns for HLH. On day 4, the patient became increasingly tachypneic and tachycardic with radiographic findings of pulmonary edema despite diuresis, as well as acute kidney injury with decreased urine output. She was intubated for increased work of breathing. Due to a high suspicion of HLH with the probability of HLH greater than 99% calculated by the HScore, methylprednisolone 120mg daily in split doses was initiated. Etoposide was not started due to her multiorgan dysfunction. On day 5, her liver and kidney failure worsened, and her ferritin and triglycerides continued to rise. She also developed hypofibrinogenemia concerning for DIC. On day 6, methylprednisolone was changed to dexamethasone 8mg Q6 and anakinra 100mg Q12 was added, but this was discontinued on day 7 when her liver biopsy showed many caseating and non-caseating granulomas with AFB stain positive for acid-fast bacilli. Sputum AFB stains were also obtained positive for acid fast bacilli. Sputum PCR showed *Mycobacterium tuberculosis* (TB) leading to the presumptive diagnosis of HLH secondary to disseminated TB. Due to the patient's acute liver failure, a modified regimen of TB treatment was initiated including rifampin, ethambutol, levofloxacin, and amikacin. Despite TB treatment, immunosuppression for HLH, and supportive measures, the patient continued to deteriorate and expired on day 10.

#### DISCUSSION

Although HLH secondary to TB (TB-HLH) has previously been reported in the medical literature, it remains a rare entity.<sup>1</sup> Most patients with TB-HLH had short symptom duration and rapid progression leading to multi-organ dysfunction and ultimately, death.

The first HLH treatment protocol was published in 1994 (HLH-94) and has been widely used in clinical practice. HLH-94 includes an anti-inflammatory agent, dexamethasone, and a pro-apoptotic agent, etoposide. This regimen has been shown to improve survival but was primarily based on data in the pediatric setting, many with primary HLH.<sup>2</sup> Furthermore, etoposide was not determined to be a safe option due to her multi-organ dysfunction. Instead, anakinra, an IL-1 receptor antagonist was used in combination of dexamethasone. Anakinra as an immuno-modulator has also been shown to be effective in the treatment of severe HLH in the critical care setting. <sup>3-4</sup>

Additionally, secondary HLH is often triggered by an acute infection or other condition (eg, rheumatologic condition) and treatment should be to address the underlying cause of immune activation. Although there is no consensus of standard treatment for TB-HLH, a systematic review of the international literature demonstrates that a delay or absence of antitubercular therapy (ATT) were associated with decreased survival.<sup>5</sup> On the contrary, the combination of antitubercular therapy (ATT) with immunotherapy has been found to significantly reduce mortality.<sup>1</sup> Our patient was initiated on a modified regimen of ATT as soon as the diagnosis of disseminated TB was made, but she still passed several days later. This case highlights the need for ongoing investigation for early detection and management of secondary HLH in the adult setting.

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## **Exploring the Adverse Effects of CAR-T Therapy:** A Case Report of Potential MINOCA in CAR-T

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#### **INTRODUCTION**

The discovery and application of Chimeric Antigen Receptor T-Cell Therapy (CAR-T) has marked a new era in cancer treatment. CAR-T is a novel therapy with a relatively small treatment population, and we have yet to identify the full spectrum of its adverse effects.<sup>1</sup> There are well-established approaches to the most common adverse effects, principally cytokine release syndrome (CRS), but there is limited literature discussing the nature of cardiotoxicity in CAR-T, much less its mechanism or management.<sup>2,3</sup> This case study discusses the development of myocardial infarction with no obstructive coronary atherosclerosis (MINOCA) in a patient treated with CAR-T.

#### **CASE PRESENTATION**

A 48-year-old man with a history of Stage IV Diffuse Large B-Cell Lymphoma refractory to R-CHOP alternating with high-dose methotrexate and cytarabine, craniospinal irradiation, and haploidentical stem cell transplant, underwent CD 19-directed CAR-T. His post-treatment course was complicated by marrow aplasia and infection, but he ultimately responded to therapy and achieved complete remission.

Five months after undergoing CAR-T, the patient presented with persistent malaise and vague abdominal pain. Initial assessment found him to be cachectic and frail, and he was admitted for further investigation of failure to thrive (FTT). An extensive workup of endocrine, metabolic, and infectious causes of FTT was unrevealing. Labs showed stable neutropenia (ANC 0.4) and anemia (Hgb 9.7) with no evidence of adrenal insufficiency, thyroid dysfunction, vitamin deficiencies, nor bacterial, viral, or fungal infections. EGD did not reveal any significant gastrointestinal pathology, only patches of chronic, mild inflammation.

On the sixth day of hospitalization, the patient reported left shoulder pain. Telemetry showed an acute increase in heart rate, from a baseline sinus tachycardia of 100-110 bpm to 130-140 bpm. EKG revealed new inferior ST segment elevations. Echocardiography identified newly depressed ejection fraction (45%) and basal to mid-anterior and anteroseptal wall motion abnormalities, where previous studies had shown normal EF and no segmental wall motion abnormalities. High-sensitivity troponins were elevated and continued to rise from – 344 ng/L followed by 366 ng/L in the setting of normal renal function. Subsequent cardiac catheterization revealed no obstructive coronary artery disease. Altogether, the evidence for myocardial injury in the absence of obstructive coronary artery disease culminated in a diagnosis of MINOCA.

A multi-disciplinary team including Cardiology and Hematology-Oncology reviewed possible etiologies of cardiac injury. Although the patient had previously received doxorubicin chemotherapy (total of 229 mg, 20 months prior to this admission), the acute onset of ST elevations and dynamic troponins were atypical for anthracycline-induced cardiomyopathy.<sup>4</sup> Similarly, the presentation was not typical for stress-induced cardiomyopathy, especially in the absence of an acute trigge.<sup>5</sup>

The constellation of cardiac findings was attributed to myocarditis, but the underlying cause remained unclear. The patient was not taking any medications commonly associated with myocarditis. Infectious workup was negative including blood cultures, urine cultures, influenza A and B, respiratory pathogen panel, EBV, CMV, tuberculosis and aspergillus testing. Of note, testing for coxsackie A and B, HIV, and HSV was not performed. Previous reports have posited a CRS-mediated mechanism of cardiac injury in CAR-T, but CRS typically peaks days after treatment, and would be uncommon months after CAR-T infusion.<sup>6</sup> Another proposed mechanism considers off-target cross-reactivity, leading to an autoimmune myocarditis.<sup>6</sup> The next best steps to workup myocarditis would have been further infectious testing, cardiac MRI, endomyocardial biopsy, but these were deferred as the patient was high-risk for invasive procedures and the findings were unlikely to change clinical management.

Besides myocarditis, other etiologies of MINOCA include coronary vasospasm, coronary microvascular dysfunction, and thrombophilia<sup>7</sup>. These were not further investigated during the patient's hospitalization.

#### DISCUSSION

CAR-T is a novel therapy with a relatively small treatment population, and we have yet to uncover the full spectrum of its effects. This case illustrates the potential for MINOCA as a result of CAR-T-induced myocarditis. Other possible etiologies of MINOCA include coronary vasospasm and coronary microvascular dysfunction, but there is no available literature on these pathologies in CAR-T. Identifying similar cases will allow for further characterization of susceptible patient populations, underlying mechanisms, and preventative strategies.

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## A Case Report Of Tragaxofusp Causing Severe Tumor Lysis Syndrome In A Patient With Blastic Plasmacytoid Dendritic Cell Neoplasm

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#### **INTRODUCTION**

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy that does not respond to cytotoxic chemotherapies well. We present a case of BPDCN that was treated with a new targeted therapy tagraxofusp and the fatal complication that the patient developed with this treatment.

#### **HOSPITAL COURSE**

The patient was an 83-year-old male without significant past medical history who presented to his primary care physician with several days of generalized malaise. He obtained routine bloodwork which showed a leukocytosis to 29 B/L. He then presented to the ED for further evaluation. Vitals were within normal limits and physical exam was remarkable for splenomegaly. Labs were significant for a WBC 44.7 B/L, Hgb 10 g/dL, platelets of 96 B/L, and the differential showed 20.6 B/L blasts. Creatinine was increased from a baseline of 1.20 to 1.45mg/dL, potassium was 4.9mmol/L, phosphate was 3.1mg/dL, calcium was 8.5 mg/dL, lactate dehydrogenase was 2705 IU/L, and uric acid was 5.1mg/ dL. A peripheral smear was done which showed immature leukocytes with blastic morphology. He was admitted for further hematologic malignancy workup.

Flow cytometry of the peripheral blood showed a population that was CD4+, CD7+(dim), CD33+(dim), CD38+(partial, bright), CD56+(partial, bright), CD 123+, HLA-DR+(bright) and a monoclonal CD5+CD23+ B cell population. These markers show an undifferentiated blast population specific for neither lymphoid nor myeloid lineage. Fluorescence in-situ hybridization (FISH) showed 17p (TP53) deletion, 13q deletion (D13S319 and LAMP1), and ZRSR2 mutations. A complete karyotype revealed multiple complex chromosomal abnormalities with the presence of two unrelated abnormal clones suggesting genomic instability as well as the clonal evolution of neoplastic cells. Bone marrow biopsy showed hypercellularity and 84% immature-appearing cells. The abnormal cells had following phenotype: CD4+, CD10, CD13-, CD14-, CD16-, CD33+ (partial, dim), CD34-, CD38+, CD56+ (partial), CD64-, CD117-, HLA-DR+. These immature cells express CD123 and were negative for MPO by peripheral blood flow cytometry. By immunohistochemistry, the neoplastic cells were positive for CD4, CD43, CD56 (dim, partial), and TCL-1 (diffuse and strong). Notably, they were negative for CD68, CD163, lysozyme, and MPO. These findings are consistent with the diagnosis of blastic plasmacytoid dendritic cell neoplasm (BDPCN). Additionally, flow cytometry detected a small monoclonal B-cell population (6%) with phenotype consistent with chronic lymphocytic leukemia/small lymphocytic lymphoma. Further assessment by computed tomography (CT) of the abdomen and pelvis revealed massive splenomegaly to 23cm but did not show evidence of metastatic disease or lymphadenopathy in the chest, abdomen, and pelvis.

The patient was subsequently started CD123 targeted therapy with tagraxofusp at a dose of 12 mcg/kg three days after admission. His lab values remained stable from admission to initiating therapy. On cycle 1. day 1, approximately 6 hours after he finished his first infusion, the patient was found to have altered mental status with increasing dyspnea and tachypnea to 50's with desaturation to 80% on room air. Labs obtained at the time showed a WBC 130.5 B/L, Hgb 9.5g/dL, platelets of 102 B/L, and the differential showed 117.5 B/L blasts. His creatinine was 2.11mg/dL, potassium 7.4mmol/L, phosphate 10.9mg/L, LDH 20119 IU/L, and urate of 5.8mg/dL. The patient was placed on non-invasive positive pressure ventilation and diuresis was given without significant improvement. The decision was made to intubate and he was transferred to the medical intensive care unit. The patient's acute hypoxic respiratory failure was thought to be due to a combination of capillary leak syndrome and tumor lysis syndrome resulting in anuric acute kidney injury and fluid retention.

After his arrival to the intensive care unit, the patient was febrile with temperature 102.4 F, hypotensive with BP 111/33, and bradycardic to 51 BPM. He was given more diuresis with IV furosemide 100mg and started on vancomycin and cefepime. Telemetry showed changes consistent with hyperkalemia including peaked T-waves and bradycardia. Temporizing measures were given including insulin, dextrose, and bicarbonate infusion. However, he ultimately required continuous veno-venous hemodialysis (CVVHD) due to the severity of his electrolyte derangements. During the patient's ICU course, he developed seizure-like activity. CT of the head was negative for any acute changes such as edema or hemorrhage. An electroencephalogram (EEG) was done but was negative for seizure activity. The patient then developed shock liver with elevations in AST 2859, ALT 2205, ALP 108, and had a lactate of 11.9. He also had multiple episodes of supraventricular tachycardia with heart rates up to 170 BPM, which required adenosine and cardiac resynchronization therapy. Due to the severity of the patient's condition and the wishes of the patient's family, aggressive care was stopped and the patient's care was switched to comfort measures only. He passed away on cycle 1, day 4, after a palliative extubation.

#### DISCUSSION

BPDCN is an aggressive hematologic malignancy. One of the characteristics of this malignancy is that the neoplastic cells almost always overexpress interleukin-3 receptor subunit alpha (IL3RA or CD123). Tagraxofusp, as a CD123-directed cytotoxin consisting of recombinant human interleukin-3 fused to a truncated diphtheria toxin, targets this overexpression specifically.<sup>1</sup> In 2019, a nonrandomized, multistage, open-label, multicenter evaluation of tagraxofusp as monotherapy in patients with BPDCN study was published in the NEJM and a 90% overall response rate was observed among patient with previously untreated BPDCN, and the majority of responses were complete remission. In contrast, prior to the development of tagraxofusp, there was no standard treatment for BPDCN. BPDCN was treated with cytotoxic chemotherapy regimens that were conventionally used for treating acute lymphoblastic leukemia/large B cell lymphoma, non-Hodgkin lymphoma, or acute myeloid leukemia but with very limited success. Although the standard-of-care remains untested in randomized fashion, tagraxofusp exhibits a higher rate of complete responses when used in the first-line setting. Because of this presumed efficacy and his advanced age putting him at higher risk for intensive induction chemotherapy, we chose tagraxofusp as our therapy of choice.

The most serious adverse events of tagraxofusp that has been reported is capillary leak syndrome.<sup>2</sup> Capillary leak syndrome is characterized by leakage of intravascular fluids into the extravascular space, leading to generalized edema, pulmonary edema and multiorgan failure. In the Pemmaraju et al study, 9 patients (19%) had capillary leak syndrome of various grade and two deaths that were attributed to capillary leak syndrome. Tumor lysis syndrome was also described as a less common and less severe adverse event of tagraxofusp in this study. In total, 11% of the patients had  $\geq$  grade 3 tumor lysis syndrome.<sup>2</sup> However, no deaths were reported to be associated with tumor lysis syndrome. In our patient's case, he developed an overwhelming response to the tragaxofusp immediately after his first dose. His anuric acute kidney injury secondary to tumor lysis syndrome led to metabolic derangements, cardiac instability and death. As potential adverse effects are not fully known for this new agent, we suggest that this case should raise awareness of the potential severity of tumor lysis syndrome with tagraxofusp. In addition, cytoreduction could be considered prior to the start of tagraxofusp in patients with high tumor burden to decrease the risks of developing tumor lysis syndrome.

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## A Case Report of Bullous Subconjunctival Hemorrhage in Adenoviral Conjunctivitis

Sean Haynie and Jesse Johnson, MD



#### **INTRODUCTION**

Subconjunctival hemorrhage is a benign and self-limiting condition that often occurs without any obvious trauma to the eye. Most cases do not cause pain or changes in vision, and thus no active management is required. We present a case of subconjunctival hemorrhage that resulted in the formation of bullae and caused significant ophthalmic morbidity in a patient on therapeutic anticoagulation with adenoviral conjunctivitis.

#### CASE

A 78-year-old female with a past medical history of optic neuropathy and atrial fibrillation on warfarin presented with two weeks of progressive bilateral eye redness, swelling, pain, and blurry vision. Initially, the patient was experiencing symptoms only in her right eye, and the contralateral eye became involved throughout the course of her illness. Examination was remarkable for bilateral bullous subconjunctival hemorrhage and trace edema of her eyelids with tenderness to palpation (Figure 1). Tonometry, computed tomography scan of the orbits, and fluorescein stain were all unrevealing. A viral respiratory pathogen panel was positive for adenovirus, and INR appropriately elevated to 2.13 on admission. Other laboratory tests were within normal limits. She was treated with carboxymethylcellulose sodium 0.5% ophthalmic solution and erythromycin 0.5% ophthalmic ointment 5mg/g three times daily, which significantly improved both her pain and blurry vision. The patient was discharged and scheduled to follow up with oculoplastics and ophthalmology.

Figure 1. Bilateral subconjunctival hemorrhage with edematous eyelids and watery discharge.

#### DISCUSSION

The conjunctiva is a thin transparent membrane that covers the sclera as well as the inner surface of the eyelid.<sup>1</sup> Inflammation of this membrane is known as conjunctivitis.<sup>1</sup> Viral conjunctivitis is typically caused by adenovirus and is the most common overall cause of infectious conjunctivitis.<sup>2</sup> The virus itself is spread through direct contact with an infected individual or their secretions as well as contaminated objects or surfaces.<sup>3</sup> Most often, patients will present with injection, watery or mucoserous discharge, and a burning or gritty sensation affecting one of their eyes.<sup>4</sup> However, it is common for the other eye to become involved within the first 24-48 hours.<sup>4</sup> This condition is self-limiting, with symptoms worsening over the first three to five days, followed by a gradual recovery over two to three weeks.<sup>4</sup> While antiviral agents are not indicated in the treatment of viral conjunctivitis, patients may benefit from the use of topical antihistamines, decongestants, or lubrication by either antibiotic or nonantibiotic ointments.<sup>1</sup> The patient in this case did not demonstrate the classic presentation of viral conjunctivitis, specifically with regard to her prolonged period of worsening symptoms, and bullous subconjunctival hemorrhage. Subconjunctival hemorrhage is a common condition and refers to bleeding into the compartment located between the conjunctiva and the episclera.5 There are many know risk factors associated with subconjunctival hemorrhage, including acute conjunctivitis, trauma, contact lens use, systemic vascular disease, and anticoagulation therapy.<sup>5,6</sup> Alternatively, bullous subconjunctival hemorrhage, marked by the presence of conjunctival bullae, is an exceedingly rare condition that is generally limited to cases of ocular trauma with scleral rupture.<sup>5</sup> To date, there appears to be no cases of non-traumatic bullous subconjunctival hemorrhage, such as that seen in our patient. Without other known risk factors, it is possible that her warfarin use, in the setting of adenoviral conjunctivitis, contributed to this unique presentation.

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Nina Mingioni, MD

## **Case Report of E-cigarette Associated Lung Injury** in a Healthy Female

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#### **CASE DESCRIPTION**

This is a case of a woman presenting with four days of diarrhea and dyspnea found to have E-cigarette or vaping-associated lung injury (EVALI).

The patient is a 30-year-old woman who presented to the hospital with a chief complaint of dyspnea on exertion. She developed dyspnea seven days prior to presentation; it was minimal at rest, however symptoms worsened with exertion. Her symptoms included fevers, intermittent chills, night sweats, dry persistent cough, and four days of profuse, watery diarrhea. She did not have sinus pain or congestion, headaches, or sore throat. Due to bloody diarrhea she sought medical care.

The patient had no allergies and took no medications regularly. She had a history of exercised-induced asthma during childhood that had resolved. Surgical history was notable for seven surgeries for bilateral breast fibroadenomas. Family history was notable for BRCA-negative breast cancer in her mother.

She works as a real estate agent, with no known specific exposures. Ten days prior to admission, she had spent time with her nephew who she reported as having several symptoms consistent with an upper respiratory infection. She does not smoke cigarettes. She had been using electronic cigarettes with marijuana for 6 months earlier in the year, however due to news reports, she had recently stopped. She would smoke marijuana from electronic cigarettes four days a week with cartridges lasting about one week. Patient used no other drugs or alcohol. No history of homelessness or incarceration. Patient is sexually active with one male partner with no prior HIV or sexually transmitted infections (STI). On review of systems, patient noted to have an unintentional 5-pound weight loss over the past one week.

On initial vital signs, she had temperature of 38.2 C, HR of 117 bpm, blood pressure of 108/74 mmHg, respiratory rate of 22 breaths/minute, 86% on ambient air and 95% on 2 liters nasal cannula of oxygen. She was admitted to the medical service due to a new oxygen requirement.

Physical exam was notable for of a well-developed and nourished adult female in no acute distress on nasal cannula able to speak in full sentences. Pulmonary exam showed scattered rales with no wheezing. She had tachycardia with no jugular venous distention. She had no abdominal pain or lower extremity swelling.



**Figure 1**. High-resolution CT of the chest demonstrating diffuse ground-glass opacities with septal thickening. There is a peripheral predilection with subpleural sparring disease.

Laboratory results on presentation revealed a leukocytosis of 28,000 cells/mm3 with 92% neutrophils and a platelet count of 558 cells/mm3. Electrolytes revealed a potassium of 2.9 mEq/L, HCO3 of 22 mEq/L. Liver function tests showed an AST/ALT of 119/73 IU/L. Lipase was normal. Lactate normal at 1.2 mmol/L. Procalcitonin was 0.64 ng/mL (normal < 0.08 ng/mL).

Respiratory pathogen panel nasopharynx swab detected human rhinovirus/enterovirus on PCR. Blood cultures showed no growth. Influenza A/B, RSV PCR nasal swab was negative. Clostridium difficile toxin DNA, and gastrointestinal stool infectious panel were negative. HIV antibody and antigen combination were non-reactive. Streptococcus pneumoniae and Legionella antigen urine



Figure 2. On the left, Romanowski stain showing numerous alveolar macrophages with abundant vacuolated cytoplasm. On the right, positive orangestained droplets within the cytoplasmic vacuoles of alveolar macrophages.

test were negative. Urine pregnancy test was negative. Urine drug screen was positive for cannabinoid.

Chest x-ray on initial evaluation revealed diffuse patchy bilateral opacities with no effusions. Right upper quadrant ultrasound was normal.

Patient was admitted and placed on azithromycin and ceftriaxone for community-acquired pneumonia. Subsequently was changed to levofloxacin 750 mg oral. Due to continued oxygen desaturation on ambient air, intermittent fevers, and tachycardia for two-day duration despite antibiotics and supportive care a high-resolution computed topography (HRCT) of the chest was obtained.

HRCT demonstrated widespread ground glass opacities and scattered septal thickening bilaterally without lobar predominance, with diffuse subpleural sparing (Figure 1). There were dense consolidations seen in the bilateral lobes and the right middle lobe. These findings were consistent with inhalation-induced lung injury as well as viral and atypical pneumoniae.

Patient subsequently underwent bronchoscopy. Findings notable for normal airway with parenchymal infiltrates. Bronchoalveolar lavage (BAL) with a transbronchial biopsy were performed. Right middle and left upper lobe BAL pathology revealed oil-red O stain showing intracytoplasmic lipid droplets in alveolar macrophages consistent with lipid laden-macrophages (**Figure 2**). Transbronchial biopsy of the left lingula showed pneumonitis; there was interstitial edema, inflammation, mild fibrosis, hyperplasia of type II pneumocytes, organizing pneumonia, and macrophages in the airspace.

The history, imaging and pathology were felt to be consistent with EVALI. Due to this the patient was placed on three days of methylprednisone 250 mg every 12 hours. Upon the second day of this regimen, she no longer had ambulatory desaturation with stable vital signs. She finished a seven-day course of antibiotics while hospitalized. She was discharged on 40 mg daily of prednisone for with subsequent pulmonary medicine outpatient visit, which has not yet occurred.

#### DISCUSSION

EVALI is lung injury due to the inhalation of non-combustible aerosol containing "nicotine, flavors, propylene glycol, and vegetable glycerin", which includes battery operated devices that include electronic cigarettes (e-cigarettes).<sup>1</sup> EVALI is becoming a more prevalent, being formally recognized in 2019, with over 2,000 cases reported in the United States by the Center for Disease Control (CDC).<sup>2.3</sup> This new clinical entity has led to interest in the pathogenesis of EVALI. Though no single agent has been implicated in the pathogenesis of EVALI, many patients have used nicotine, tetrahydrocannabinol (THC), and cannabinoid (CBD) oils.<sup>2.4</sup> Another agent of interest implicated in in the pathogenesis of EVALI is vitamin E acetate, which has been associated with impairment of pulmonary surfactant.<sup>5.6</sup>

EVALI is a type of acute lung-injury presenting with a wide-range of pulmonary complaints and findings. The most common presenting symptoms fevers, tachycardiac, and tachypnea.<sup>4</sup> One review revealed gastrointestinal symptoms in about 80% of patients. In this same review, 67% of patients presented with hypoxemia, and about 30% of patients had oxygen saturation less than 88%.<sup>4</sup> Chest imaging generally reveals marked bilateral opacities. The typical chest CT finding is ground glass opacities marked by subpleural sparing.<sup>47</sup> These findings, however, can be seen in other pathological process and thus may warrant

further investigations with bronchoscopy and BAL. EVALI leads to alveolar damage and fibrinous pneumonitis and has a wide range of histopathological findings. Most reported cases involve variation in cell counts from BAL, though usually with a predominance of neutrophils.<sup>4</sup> Many cases report Oil-red-O staining lipid-laden macrophages as in this patient.<sup>8</sup>

One confounding variable in this case was a positive rhinovirus/enterovirus test, which could explain some of her symptoms. However, it is unlikely that this viral infection would have produced such significant clinical decompensation in an otherwise young and healthy patient. Moreover, clinical history, ground glass opacities with subpleural sparing, and lipid-laden macrophages with pneumonitis are consistent with our current understanding of EVALI.

#### CONCLUSION

In patients who present with respiratory complaints and history of E-cigarettes, EVALI should be strongly considered. This is particularly true in those with hypoxemia and respiratory distress. A chest CT is an Important diagnostic modality to help identify and inhalation pattern injury, but many patients may need further testing with bronchoscopy and BAL. We presented a case of a young, healthy patient who had significant respiratory distress secondary to EVALI.

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## Serum Ammonia and Folate Levels: Opportunities for High Value Care

R. Benson Jones Jr. MD, Sean Dikdan MD, and Bracken Babula, MD

High value care encompasses a variety of principles including ordering tests with high diagnostic yield, while reducing low value practices. Two tests that are frequently ordered but rarely contribute meaningfully to the diagnosis and management of patients are serum ammonia levels and serum folate levels. The American Association for the Study of Liver Disease (AASLD) recommends against using blood ammonia levels for hepatic encephalopathy (HE), stating that the test does not add "any diagnostic, staging, or prognostic value" for patients with chronic liver disease<sup>1</sup>. The American Society for Clinical Pathology (ASCP) in the Choosing Wisely campaign by the American Board of Internal Medicine recommended considering "folate supplementation instead of serum folate testing in patients with macrocytic anemia<sup>2</sup>." In the following discussion, we will discuss the evidence behind these claims in addition to our own argument against routinely ordering serum ammonia and serum folate levels in the assessment of hepatic encephalopathy and anemia, respectively. We will also provide a preliminary analysis of the cost related to these tests and the potential impact of changing ordering practices at our institution, a large urban academic medical system.

## Serum Ammonia Levels in the Assessment of Hepatic Encephalopathy

HE is a brain dysfunction caused by liver pathology, portosystemic shunting, or both. It manifests in a wide spectrum of neurological and psychiatric abnormalities and is typically a clinical diagnosis using the West Haven Criteria (WHC) classification system<sup>1</sup>. Because 85% of ammonia is detoxified by the liver and excreted as urea in urine (with muscle and brain tissue metabolizing the rest), it has been theorized that hyperammonemia contributes to HE<sup>3</sup>. Astrocytes synthesize more glutamine in the setting of increased ammonia, precipitating reactive oxygen species, astrocyte swelling, and enhanced gamma-aminobutryic acid (GABA) inhibition, manifesting as cerebral dysfunction. In addition, bleeding, infection, and renal failure all precipitate HE and incidentally promote hyperammonemia. With these underlying factors in mind, it would appear that ammonia levels would be helpful in the diagnosis of HE. Multiple issues with serum ammonia, however, limit its usefulness. Fist clenching, the use of a tourniquet during the process of phlebotomy and processing time can lead to false elevations or spurious results<sup>4-6</sup>. The sensitivity and specificity of a venous ammonia greater than 55 µmol/L) to diagnose HE were 47.2% and 78.4%, respectively. In one study, 60% of the patients with grade 3 HE by the West Haven Criteria had a normal serum ammonia level<sup>7</sup>. These test characteristics underlie the AASLD recommendation to avoid checking serum ammonia in patients with chronic liver disease to diagnose or assess the severity of HE. Covert HE (i.e. Grade I HE by WHC) remains a diagnostic challenge given the lack of reproducibility of clinical findings, but trivial lack of awareness, shortened attention span, and altered sleep rhythm can raise suspicion for this diagnosis in patients with liver disease.

## Institutional ordering characteristics and associated healthcare charges for serum ammonia

Between the initial date of data recording (11/25/2016) to the day the database was accessed (1/14/2020), there were a total of 7541 serum ammonia orders. Of these orders, 6206 orders occurred in the inpatient setting, with a charge of \$201 per order according to the publicly available institutional chargemaster<sup>8</sup> (Figure 1). Note that these charges do not reflect what the patient pays; insurance companies dictate how much reimbursement the institution receives. The average dollar amount of charges per month attributable to inpatient serum ammonia orders alone is \$31,984.76, calculated by dividing the total charge amount for all serum ammonia orders over the examined time (\$1,247,406) by the number of months of data (39 months). The departments who ordered the most serum ammonia levels are Medicine (2404 orders total), Emergency Medicine in the flagship hospital (1702), and Emergency Medicine in a nearby community hospital (702) (Figure 2).

## Serum Folate Levels in the Assessment of Anemia

Folic acid (folate) is a critical water-soluble B vitamin used in the process of DNA synthesis. Deficiency of folate manifests in newborns as neural tube defects and classically as macrocytic, megaloblastic anemia in adults. In an effort to reduce the incidence of neural tube defects, the US government began mandating supplementation of every 1 gram of grain with 140 mcg





Figure 2



Figure 3



of folic acid in 1996, leading to a 36% reduction in the prevalence of neural tube defects in the US.<sup>9</sup> This fortification has led to a significant decline in prevalence of adult folate deficiency. In an analysis of the National Health and Nutrition Examination Survey (NHANES) study group, Pfeiffer and colleagues found that "the percentage of the population with low serum folate (<3 ng/mL) declined from 21% in the period before fortification (1988--1994) to <1% of the total population in the period immediately following fortification<sup>10</sup> (1999--2000)." Despite low prevalence of folate deficiency clinicians continue to order the assay, which

has its own innate flaws. Although the microbiologic assay for serum folate is more accurate and the gold standard, the competitive protein binding assay is more frequently used due to its relative technical ease. Unfortunately this protein binding assay has a coefficient of variance between samples from the same individuals of 21.5%<sup>11</sup>. Finally, the cost of treatment of folate deficiency is orders of magnitude less expensive than the assay itself: 400 mcg folate tablets range from \$0.03 per tablet to \$0.20 cents per tablet, while the charge for the folate assay ranges from \$25 in outpatient assistance programs from commercial laboratory corporations to \$207 by the institutional chargemaster<sup>8, 12</sup> (Serum folate assay pricing, LabCorp<sup>®</sup> and Quest Diagnostics Customer Service, phone call, 1/14/2020). Thus, when a macrocytic anemia and the suspicion for an isolated folate deficiency is high (malabsorptive issues, prior GI surgery, prolonged malnutrition), it is reasonable to initiate folate supplementation and to recheck a complete blood count in 4 weeks to see if the MCV and anemia has changed<sup>13</sup>.

## Institutional ordering characteristics and associated healthcare charges for serum folate

With the same criteria as the prior analysis, there were 43,932 total serum folate and combined serum folate and vitamin B12 orders. Of these orders, 7193 were serum folate alone. The Department of Medicine ordered 33,451 (76.1%) of the total orders (**Figure 3**). The total charge per month for serum folate orders was estimated to be between \$28,161.53 and \$233,177.53 using the \$25 charge from commercial laboratory and the \$207 charge from the institutional chargemaster to generate the range. Note that the \$25 charge is a direct cost to the patient, while the \$207 is the charge submitted to insurance companies.

#### CONCLUSION

Serum ammonia and serum folate levels should not be routinely ordered in the diagnosis and management of hepatic encephalopathy or in the diagnosis of anemia, respectively. Chargemaster charges and simple numerical counts of orders shows a significant charge burden for tests that do not significantly impact patient care. While this analysis does not provide cost estimates to the institution as a whole as it does not incorporate assay costs and lab personnel processing time, it reveals the charges that minimal utility tests impose on the healthcare system. One proposal to reduce ordering folate levels is to replace the combined folate/B12 order with individual folate and B12 orders in physician preference lists. Future work will assess the impact of iterative changes on the reduction of these orders and strive to understand the cost of these assays to the institution.

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## **Refusing to be Labeled**

#### Jennifer Perugini

The tension in the room was palpable as ankles bounced feet and charged glances were shared from across tables. About 15 of my medical school peers were listening to a lecture on plastic surgery and reconstruction techniques, however 'listening' may be a generous term for what we were doing. There was only one thing running through every brain in that room: will it be high enough? We were anxiously awaiting our USMLE Step 1 scores. I looked around the room and, like me, almost everyone had their cell phone resting in their lap, trying not to make it too obvious that a webpage was being refreshed every few seconds. One by one my classmates took turns slipping outside to watch a number pop up on a small screen - a number we had been programmed to associate with our future success, or lack thereof. Had we chosen enough correct answers on that fateful exam to be destined for greatness or were we doomed to an insignificant career in a land far, far away?

The USMLE Step 1 exam had been so hyped up in my first two years of medical school that I almost couldn't remember a time when the results of the exam weren't at the forefront of my mind. The test was brought up during my interview day, during the second-look event I had attended, in our first welcome address upon arriving on campus, and in every course henceforth. The importance of the assessment, by the time I reached the end of my second year, had been so ingrained that when my family asked what I was studying for I almost gaped with incredulousness. "You mean you don't know what Step 1 is?", I proclaimed, eyebrows shooting upward. "This is the exam that will determine the rest of my life – it will dictate what type of doctor I can be and where I can train!" Despite my best efforts, I couldn't quite seem to get my point across. My parents, having no exposure whatsoever to the drawn-out process of becoming a doctor, couldn't understand the monumental gravity of this single exam, this one number on a tiny cell phone screen. They were taken aback that one score could dictate so much - and honestly, I couldn't quite justify it myself.

My own journey into the field of medicine began from a very young age. I did not come from a family of physicians or overcome a serious childhood illness leading to a sacrosanct devotion to the field. I was, however, taken on an annual hospital pilgrimage on my birthday to stare, on tiptoes, at the newborns who would forever share my same date and location of birth. Each one was carefully swaddled in that iconic white receiving blanket with blue and pink stripes that, despite the ever-changing medical field, has remained a familiar constant—the global signifier of hospital birth. I understood that I might never meet these tiny humans or even ever know their names, yet somehow, I still felt a strong sense of connection. Though new HIPAA laws eventually curtailed my yearly visits to the hospital nursery, I had already been jump-started on my medical journey. Whether it was candy-striping in high school, interning in an Italian eye clinic in college, or distributing mosquito nets in remote villages of Laos after graduation, my passion for clinical care never wavered. It is with this same sustained dedication that I have navigated medical school, and it is how I will approach each day as an intern and resident physician.

I didn't score highly on Step 1 of the USMLE. Writing these words or even worse – being forced to say them out loud – pings the edges of my heart the way muscle jumps backwards from the sting of cautery. From the very first moment I saw those three digits, I have felt branded with a mark of incompetence. I have envisioned a bubble above my head that stays with me wherever I go, obstinately displaying my worth for the world to see. I have been turned down from elective rotations, passively dismissed from residency interviews, and even told by one mentor that I am "not cut out for a surgical subspecialty based on [my] Step 1 score."

It has taken me a lot of time, and a lot of reflection, to come to terms with the fact that my future, let alone my self-worth, will not be determined by one exam I took during medical school. I have honored almost all of my clinical rotations, have received heartfelt letters from patients sharing gratitude for being the only person to truly listen to them, have sought out medical opportunities on four continents in two languages, and have volunteered with some of the most vulnerable populations in society. Numeric scores aside, I refuse to believe that I will be anything less than the skilled, hardworking, and compassionate Obstetrician Gynecologist that I can envision so clearly.

As a medical community, by marginalizing students who perform below average on USMLE testing, we stifle passion and creativity. By telling students that they are not qualified for a certain specialty based on a test score, we smother confidence and stifle spirits. And when it comes to the best interest of our patients, are we not doing them a disservice by attempting to filter out people with lower scores, despite the energy and passion those students may bring to the field? I hope to be the kind of intern, resident, and future attending OB-GYN that encourages students, regardless of USMLE scores, to pursue the specialty that most speaks to them, the patient population they feel most empathy for, and the disease processes that make them feel intellectually vitalized. I felt all of these things, and more, when I discovered my passion for OB-GYN. For a medical student, discovering one's specialty of choice sparks a feeling comparable to coming home after a long, long time away. And who are we, as medical professionals, to quell such a feeling?

Much to Jennifer's contentment, the score reporting policy for Step 1 of the USMLE was changed from three-digit reporting to pass/fail reporting shortly after she wrote this piece. This policy change is to be implemented in January 2022.

#### REFERENCES

1. "Change to Pass/Fail Score Reporting for Step 1." *United States Medical Licensing Examination*, Feb. 2020, www.usmle.org/inCus/.



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