TRIPLER ARMY MEDICAL CENTER RESEARCH SYMPOSIUM

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Tripler Army Medical Center Research Symposium

Dale S. Vincent MD, MPH, MACM

For more than eighteen years, the Tripler Army Medical Center Department of Clinical Investigation has held an annual research day that highlights scholarly activities from twelve graduate medical education programs at the institution. The research day was named after James W. Bass MD, MPH, a prolific clinician-researcher in pediatric infectious diseases who was Chief of the Department of Pediatrics at Tripler and Professor of Pediatrics at the John A. Burns School of Medicine during the period 1975 to 1994. Later, the research day expanded to include clinical vignettes and quality improvement in poster sessions named after Donald A. Person MD, Chief of the Departments of Pediatrics (1994-1997) and Clinical Investigation (1997-2001) at Tripler and an eminent pediatric rheumatologist. Both men established a culture of inquiry and scientific rigor that set a standard of excellence for countless residents and fellows whom they trained. The papers in this supplement are presented as a testimony to their legacy of scholarship through service to the people of the Hawai‘i and the Pacific Rim.

Disclaimer
The views expressed in this abstract are those of the author and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

Conflict of Interest
The author does not report any conflicts of interest.

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Adult-Onset Still’s Disease: Is This Truly a Diagnosis of Exclusion?

Caleb W. Anderson MD; Phalgun A. Shah MBBS; and Jefferson R. Roberts MD

Abstract
Adult-onset Still’s Disease is a rare, idiopathic, inflammatory disorder characterized by arthralgia, evanescent, salmon-colored rash, and daily fevers as well as lymphadenopathy, pharyngitis, splenomegaly, myalgias, and serositis. The inciting etiology of this syndrome is unknown, though it has been hypothesized that infection triggers an autoimmune response. The Yamaguchi Criteria, the most sensitive and widely used diagnostic criteria, requires both a minimum set of criteria to be met as well other potential etiologies to be excluded. By definition, evidence of concomitant infection, malignancy, vasculitis, or connective tissue disease precludes the diagnosis of Adult-onset Still’s Disease from being made. We present a very rare case of a patient who met all diagnostic criteria for Adult-onset Still’s Disease, had a protracted course refractory to numerous immunsuppressant treatments, and also had evidence of coxsackie B infection with fourfold rise in viral titers on two occasions (both associated with disease flare). Although coxsackie B virus has been linked to Adult-onset Still’s Disease at disease presentation, this case is unique in its protracted course and serological evidence of infection temporally related to disease flare. While accepted diagnostic criteria call for this disease to be a diagnosis of exclusion, our case supports the fact that ongoing infection may in fact be an important antigenic driver in persistent and refractory Adult-onset Still’s Disease.

Keywords
Still’s Disease, Adult-Onset/diagnosis

Introduction
Adult-onset Still’s disease (AOSD) is a rare, idiopathic, inflammatory disorder characterized by arthralgia, evanescent, salmon-colored rash, and daily fevers. Lymphadenopathy, pharyngitis, splenomegaly, myalgias, and serositis are also commonly seen with this disease. Frequently seen laboratory abnormalities include leukocytosis, transaminitis, elevated ferritin levels, increased acute phase reactant concentrations, and aberrant production of proinflammatory cytokines. While the inciting etiology of this syndrome is unknown, both viruses and bacteria have been isolated in patients with AOSD leading to the hypothesis that infection triggers an autoimmune response. A number of different diagnostic criteria have been published, with the most sensitive and widely used being the Yamaguchi Criteria. However, this set of criteria requires both a certain number of major and minor criteria to be met as well other potential etiologies to be excluded, as demonstrated in Table 1. Thus, by definition, evidence of concomitant infection, malignancy, vasculitis, or connective tissue disease precludes the diagnosis of AOSD from being made. We present a rare and interesting case in which a patient met all major criteria and three of the four minor criteria (and later in his disease met the fourth minor criteria), yet had proven coxsackie B viral infection with fourfold rise in antibody titer. His disease was atypical as it remained refractory for over eighteen months to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), oral disease modifying antirheumatic drugs (DMARDs) (except for prednisone), TNF-alpha agents, and anakinra. A disease flare over one year into treatment was associated with repeat fourfold rise in coxsackie B titer, though he definitively responded to initiation of tocilizumab several months after this flare. It has been hypothesized that an infectious etiology initiates a cascade of immunological insults which results in the clinical syndrome of AOSD. Investigators in the past have demonstrated persistence of viral antigens in patients with AOSD, thus raising the question of antigenic stimulation driving the ongoing immune response. We present the following case of a patient with classic AOSD and elevated coxsackie B viral titers on two separate occasions (both associated with increased disease activity) as further evidence that continuing antigenic stimulation is a driving force in refractory disease, and that AOSD may not truly be a diagnosis of exclusion.

Case
A 29-year-old previously healthy Puerto Rican man presented with pharyngitis (culture negative), chills, and knee pain. The patient was empirically treated with doxycycline followed by azithromycin though his symptoms continued to worsen. He was admitted to inpatient care at that time and was noted to have documented fever to 39.4°C, an evanescent rash of the inner thighs which spread to his arms and chest, myalgias, arthralgias with joint effusion, and pleuritic chest pain with an echocardiogram showing pericardial effusion. Labs were notable for elevated CRP to 32mg/L, ESR greater than 100mm/hr, negative ANA/RF, leukocytosis, transaminisits, ferritin of 3596 mcg/L, and elevated coxsackie B viral titre (B4 1:160, drawn 11 days into his illness). The patient’s diagnosis was initially unclear as he met four major and three minor Yamaguchi criteria in the setting of elevated coxsackie B viral titers. He was initially started on naproxen 500mg twice daily to which he responded well, though with residual symptoms for which he was switched to prednisone 40 mg/day. A coxsackie B viral panel drawn ten days after the initial panel demonstrated fourfold increase of coxsackie B3 from 1:40 to 1:160, with continued elevation of B4 at >1:160, as demonstrated in Table 2. The patient’s symptoms initially responded to high dose prednisone with decrease in ESR to 5mm/hour 121 days after disease onset. coxsackie B titer drawn 151 days after disease onset showed decreasing B3 and B4 serotypes, as demonstrated in Table 2. He was definitively
Table 1. Yamaguchi Criteria

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;39°C of one week or longer</td>
<td>Sore throat</td>
</tr>
<tr>
<td>Arthralgia or arthritis of greater than 2 weeks</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Typical Rash</td>
<td>Hepatomegaly/Splenomegaly</td>
</tr>
<tr>
<td>Leukocytosis &gt;10,000/mm^3</td>
<td>Abnormal liver function tests</td>
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</table>

Exclusion Criteria

- Negative antinuclear antibody and RF
- Infections
- Malignancies
- Other rheumatic disease

Table 2. Coxsackie B Viral Titers

<table>
<thead>
<tr>
<th>Coxsackievirus Serotype</th>
<th>Day 11</th>
<th>Day 21</th>
<th>Day 151</th>
<th>Day 471</th>
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<tr>
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<td>&lt;1:10</td>
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<tr>
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<td>&lt;1:10</td>
<td>&lt;1:10</td>
<td>&lt;1:10</td>
</tr>
<tr>
<td>Coxsackievirus B1 Ab</td>
<td>1:40</td>
<td>1:160</td>
<td>1:10</td>
<td>1:160</td>
</tr>
<tr>
<td>Coxsackievirus B1 Ab</td>
<td>1:160</td>
<td>1:160</td>
<td>1:80</td>
<td>&gt;1:640</td>
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<tr>
<td>Coxsackievirus B1 Ab</td>
<td>1:10</td>
<td>1:40</td>
<td>&lt;1:10</td>
<td>&gt;=1:640</td>
</tr>
<tr>
<td>Coxsackievirus B1 Ab</td>
<td>&lt;1:10</td>
<td>&lt;1:10</td>
<td>&lt;1:10</td>
<td>&lt;1:10</td>
</tr>
</tbody>
</table>

Figure 1. Extensive Synovitis and Soft Tissue Swelling of Left Hand.

The patient was finally tried on tocilizumab in combination with methotrexate which led to an extended disease remission that has persisted for over two years despite complete steroid taper.

Discussion

Adult onset Still’s disease is a rare, multisystem inflammatory disorder characterized by arthralgia, evanescent, salmon-colored rash, and daily fevers. While the true etiology and pathology of the disease process is not well defined, it is likely multifactorial and the result of complex interplay between host factors and antigenic insults. The immunopathogenic mechanism of this disease can be seen with elevated levels of proinflammatory cytokines such as tumor necrosis factor-alpha, interferon-gamma, interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-18. Given the abrupt onset of symptoms and high fever, an infectious etiology has been postulated. A study in Nijmegen,
Netherlands evaluated for potential infectious etiology through broad serological evaluation in five patients with AOSD. Two of the cases were thought to be secondary to rubella reinfection (based upon high IgG titres) while the disease in a third patient was attributed to Echovirus 7 as supported by positive culture from a throat swab as well as four-fold antibody titer increase. Another study evaluated 19 children with chronic rheumatic disease and isolated rubella virus from the lymphoreticular cells of seven of these patients, including one with Still’s Disease. Other implicated viruses include cytomegalovirus, Epstein-Barr virus, parainfluenza, parovirus B19, human immunodeficiency virus, hepatitis A, B, and C virus, adenovirus, human herpes virus 6 and coxsackie B virus. Bacterial infectious agents to include *Yersinia enterocolitica*, *Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Campylobacter jejuni*, and *Mycoplasma pneumoniae* have also been implicated.

Coxsackie B virus, an enterovirus consisting of an icosahedral capsid surrounding a single-stranded RNA genome, is a well known cause of febrile arthritis. Acute coxsackie viral infection is oftentimes indistinguishable from AOSD, and there have been few reports discussing the presence of coxsackie infection in patients ultimately diagnosed with Still’s disease. One study from 1983 evaluating three patients with febrile arthritis found elevated but stable coxsackie B antibody titer in two patients and a fourfold rise in viral titer in a third patient. A study from 1986 found significant rise in neutralizing antibody to coxsackie B4 virus in two patients with evanescent macular rash, constitutional symptoms, high spiking fever, and polyarthritis/
synovitis. Both patients also had elevated inflammatory markers, transaminitis, and neutrophilic leukocytosis. A case of Still’s disease and elevated initial titers to coxsackie B2 and B4 with progression to hemophagocytic syndrome was described in a 12-year-old girl in New Zealand in 1985. Our case is unique in the prolonged and refractory nature of the disease with elevated coxsackie B titers noted twice during the course, both times temporally associated with increased disease activity. These findings support either coxsackie viral reactivation or viral persistence/chronic infection as an antigenic driver to the immune dysregulation inherent to AOSD. Persistent enteroviral infection has been implicated in several chronic diseases to include insulin-dependent diabetes mellitus, dilated cardiomyopathy, chronic inflammatory myopathy, and chronic fatigue syndrome. This has been shown in both humans as well as animal models. Persistence of coxsackie virus B3 was noted in both the acute and chronic phase of myocarditis in an immunocompetent mouse model. Another study evaluating eight patients with chronic fatigue syndrome and positive enteroviral sequences by PCR were evaluated for viral persistence at a five-month interval. Four of the eight patients were found to have an identical nucleotide sequence in both samples, which was indicative of viral persistence as opposed to reinfection. While no study has directly addressed persistence of coxsackie virus in patients with AOSD, a previous study from 1994 found that AOSD patients carry a four-fold greater load of rubella viral genome than do normal controls, and that the genome is found primarily in monocytes and B cells. This suggests the possibility that patients suffering from AOSD may be unable to effectively clear viral infection from their mononuclear cells.

While our case is unique in describing elevated coxsackie viral titers temporally associated with increased disease activity, it does not definitively prove the presence of coxsackie infection as neutralizing antibody titer against coxsackie B virus lacks specificity. Viral culture or PCR would have offered more definitive evidence of infection. Also, nucleotide sequence by PCR would have been useful in determining whether the patient had persistent infection versus reinfection at the time of his disease flare.

**Conclusion**

While previous reports have associated AOSD with infectious triggers, there have been relatively few reported cases of concomitant coxsackie B infection. This case is unique in reporting a four-fold rise in coxsackie B antibody titers on two separate occasions during a prolonged, refractory course of AOSD, both temporally associated with disease flare. Previous literature has established that coxsackie B can persist in a number of chronic infections, though this has not been proven with AOSD. While the low specificity of viral titers in our case cannot prove the link between coxsackie infection and increased disease activity in AOSD, it supports that evidence of coxsackie B infection should potentially be considered an antigenic driver of AOSD rather than an exclusion criteria.

**Disclaimer**

The views expressed in this abstract/manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

**Conflict of Interest**

None of the authors identify a conflict of interest.

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**References**

Spontaneous Endometriosis Within a Primary Umbilical Hernia

Nicole R. Laferriere MD and Christopher G. Yheulon MD

Abstract
Umbilical hernias are rather common in the General Surgery clinic; however, endometriosis of an umbilical hernia is rare. It is especially unusual to have endometriosis of an umbilical hernia spontaneously occur compared to occurring at a site of a prior surgery. We present a case of spontaneous endometriosis of an umbilical hernia without prior surgery to her umbilicus. She had not presented with the usual symptoms of endometriosis and it was not considered as a diagnosis prior to surgery. Umbilical endometriosis is rare but usually occurs after prior laparoscopic surgery. We believe this is the second reported case in the English literature and the first such case reported from North America of spontaneous endometriosis of an umbilical hernia. This case highlights the importance of a full review of systems and qualifying the type and occurrence of pain. Additionally, it is always important to analyze surgical specimens in pathology to avoid errors in diagnosis.

Keywords
umbilical hernia, endometriosis, primary hernia, umbilical

Introduction
Umbilical hernia repairs are very common procedures for general surgeons. It is the second most common hernia procedure after inguinal hernia repairs. Ninety percent of adult umbilical hernias are acquired. Risk factors for an umbilical hernia include conditions that increase intra-abdominal pressure such as COPD, constipation, obesity, and multiparity. Endometriosis of an umbilical hernia is exceptionally rare, noted to only occur in 0.5-1% of all patients with endometrial ectopia. Here we discuss such a case.

Case Presentation
A 34-year-old woman presented to the general surgery clinic with a six year history of an umbilical bulge and pain two to three times per month. Her only pertinent medical history was two prior Cesarean sections with the last performed ten years prior. She denied any prior laparoscopic procedures or surgeries on her umbilicus. The bulge had not grown in size, but had become more bothersome over time. Physical exam revealed a 1 cm non-reducible hernia at the umbilicus. Abdominal ultrasound (Figure 1) showed a 1.7 x 1.5 x 1.3 cm fat containing hernia arising from a sub-centimeter fascial defect.

The patient went to the operating room for an elective open umbilical hernia repair. There appeared to be a small amount of incarcerated pre-peritoneal fat within a 1 cm fascial defect. The fat could not be reduced and was thus resected and sent to pathology. The hernia itself was primarily repaired without difficulty.

Unexpectedly, pathology analysis (Figure 2) revealed endometriosis involving fat and connective tissue. Upon further questioning at her post-operative visit, the patient noted that her umbilical pain did significantly worsen during her menstrual cycles with associated lower abdominal and pelvic pain. She was ultimately referred to the gynecology service for further management of her endometriosis.

Discussion
Endometriosis is a benign condition with endometrial glands and stroma outside the normal uterine cavity. Endometriosis is estimated to affect approximately 5%-15% of women, and most patients are in their fourth decade of life. It is often accompanied with infertility and catamenial abdominal pain. Endometriosis most commonly occurs in the pelvis, involving the ovaries, broad ligament, recto-sigmoid colon, and the appendix. The condition can also develop in surgical scars, especially after C-sections and in laparoscopic port sites, but occasionally occurs spontaneously. Umbilical endometriosis is only estimated to occur in 0.5%-1% of all patients with endometrial ectopia. Although there have been over 120 cases of umbilical endometriosis reported, this is only the fifth reported case of spontaneous umbilical endometriosis within a primary umbilical hernia. However, this is only the second reported case in the English literature and the first such case reported from North America.

Conclusion
Surgical site associated umbilical endometriosis is rare and spontaneous umbilical endometriosis is even more so. It is important to elicit a thorough history from the patient, specifically inquiring about the occurrence of pain, whether it is cyclic and worse during her menstrual cycles. Endometriosis can be easily mistaken for incarcerated pre-peritoneal fat and any suspicion should prompt a resection and pathologic examination. This patient will be referred to gynecology for further evaluation of endometriosis as a cause of her cyclic pelvic pain.
Figure 1. The ultrasound demonstrates a 1.7 x 1.5 x 1.3cm pocket containing herniated tissue contiguous and isoechoic to the peritoneal fat via a subcentimeter fascial defect. No signs of incarcerated bowel. Impression: Uncomplicated fat-containing umbilical hernia.

Figure 2. The excised tissue has scattered foci of endometrial tissue, including gland epithelium and stroma, with associated inflammation and scarring.
Disclaimer
The views expressed in this case report are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

Conflict of Interest
The authors declare that there are no conflicts of interest regarding the publication of this paper.

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References
Next-Generation Gene Sequencing Differentiates Hypoplastic Myelodysplastic Syndrome from Aplastic Anemia

Jeffrey L. Lew MD; Joshua L. Fenderson MD; and Mark G. Carmichael MD

Abstract
Hypoplastic Myelodysplastic Syndrome (h-MDS) comprises 15% of all MDS and has traditionally been difficult to distinguish from aplastic anemia (AA) by current testing. Accurate differentiation is important because treatment and prognosis differ. Since the publication of the 2008 World Health Organization classification of MDS, next-generation DNA sequencing has discovered novel mutations strongly associated with AA and MDS. Recent research supports the utility of identifying these mutations in the diagnosis and management of MDS; however, use of next-generation sequencing is not yet recommended in guidelines and the study is not routinely performed. We present a case where next-generation sequencing performed on a peripheral blood specimen aided the diagnosis and management of a 74-year-old man with h-MDS. This case adds to the growing body of evidence supporting the utility of next-generation DNA sequencing in the evaluation of MDS and h-MDS, particularly when diagnosis remains unclear after standard testing.

Keywords
Anemia, Aplastic/genetics

Introduction
Approximately 15% of all myelodysplastic syndromes (MDS) is the hypoplastic subtype (h-MDS). H-MDS is a clinically distinct entity from MDS because it is characterized by a hypocellular marrow rather than the hyperprolific/dysplastic hematopoietic cells found in MDS. The etiology of h-MDS is not well understood but it is related to autoimmune activity of increased oligoclonal T-cell expansion and suppression of hematopoietic precursors by cytotoxic T-cells. Aplastic anemia (AA) is a distinct clinical entity from h-MDS that can result in pancytopenia and severely hypocellular marrow. Morphologically h-MDS and AA are very different to differentiate by pathologists. There are criteria for diagnosing and classifying AA, and there are 2008 WHO guidelines for diagnosis and classification of MDS, however there are not clearly defined criteria to diagnose the h-MDS subtype. Although some criteria have been proposed to diagnose h-MDS, they have not been tested extensively. As a result, dependence on morphology alone is prone to interobserver variability and error. This is a problem because accurate differentiation is important as prognosis differ between h-MDS and AA. h-MDS can progress to AML more frequently than AA. In addition, the treatments of h-MDS and AA are different. While first line treatment with immunosuppressive therapy (IST) is similar for both diseases, second and third-line therapies are different and the supportive therapies are different. Hematopoietic growth factors such as GM-CSF and erythropoietin can benefit patients with MDS but will not work for patients with AA. In addition, there is evidence suggesting that response rates may be lower for IST’s in h-MDS compared to AA.

A large body of research the last decade has demonstrated cytogenetic abnormalities found in both AA and h-MDS. These cytogenetic abnormalities have been documented and incorporated into the IPSS-R for calculation of risk and survival for MDS, however new cytogenetic abnormalities, and molecular genetic abnormalities have been discovered since these criteria were established. Using targeted gene sequencing and single nucleotide polymorphism (SNP) multiple genes have been discovered that are related to MDS showing different prognostic information independent of the IPSS-R scoring system. The prognostic information of these gene mutations can range from benign to poor overall survival. For example, mutations in MDS driver genes (TP53, ASXL1, DNMT3A, EZH2 and RUNX1) were associated with lower overall survival. In addition, some mutations can help classify the subtype of MDS because they are associated with clinical phenotypes such as SF3B1 which is strongly associated with ringed sideroblasts.

Next-generation DNA Sequencing is a molecular genetic tool that uses probes to sequence specific targeted areas. This technology has previously discovered novel AA and MDS associated mutations, but their utility in the clinical setting remains unclear. We present a case where next-generation sequencing performed on a peripheral blood specimen aided the diagnosis and management of a patient with h-MDS.

Case
A 74-year-old man with three-year history of asymptomatic pancytopenia presented with fatigue, anorexia, and 10 lb. weight loss over 6-months. Vital signs and physical exam were unremarkable. CBC revealed progression of pancytopenia compared to previously stable three-year ranges. A new mild normocytic anemia with reticulocyte index indicative of inappropriate marrow response was noted. Blood smear showed rare teardrop cells and elliptocytes without dysplasia. Bone marrow evaluation revealed low normal cellularity at 25% with diminished myeloid maturation, erythroid hyperplasia, and decreased and dysmorphic megakaryocytes. These findings raised concern for aplastic anemia or hypoplastic MDS, but neither were definitively diagnosed. Chromosome analysis and MDS panel (FISH) were normal. Infectious, autoimmune, nutritional, metabolic and other malignant etiologies of pancytopenia were also excluded. Repeat bone marrow showed a progressive decline in cellularity (10%) compared to the study 6-months earlier with otherwise similar cellular characteristics. Repeat MDS panel was normal and additional testing for MDS/AML associated gene mutations was negative (table 1).
At this point, an evolving AA was favored over h-MDS, but diagnostic criteria were not met for either condition. A peripheral blood specimen was submitted for next-generation DNA sequencing of 42 leukemia associated genes (Table 2). These genes were known to have associations with leukemia, prognostic information, and response to therapy. Pathologic mutations in the RUNX1 and SF3B1 genes were identified which strongly favored h-MDS over AA. Treatment with immunosuppressive therapy was then selected based on likelihood of response in h-MDS patients with HLA-DR15 subtype which the patient had.

Table 1: Summary of patient’s studies to include CBC, Marrow exam, cytogenetic studies, molecular studies.

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>RESULTS</th>
<th>ASSESSMENT</th>
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<tbody>
<tr>
<td>Baseline Past 3-Yrs</td>
<td>WBC 2.6-4.0, Hgb 13.1-14.3, Plt 100-125</td>
<td>Pancytopenia</td>
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<td>ANC 1200-2500</td>
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<td>Presentation</td>
<td>CBC WBC 2.7, Hgb 12.4, Plt 82</td>
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<td>Blood smear – pancytopenia, no blasts or</td>
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</tr>
<tr>
<td></td>
<td>dysmorphic cells</td>
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<td></td>
<td>Bone Marrow – 25% cellularity, low myeloid</td>
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<tr>
<td>6-Month Follow-Up</td>
<td>WBC 1.9, Hgb 11.9, Plt 68</td>
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<td>ANC 470, RPI 1.22</td>
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<td>Next-Gen Sequencing</td>
<td>RUNX1 and SF3B1 mutations</td>
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Table 2. List of 42 target genes sequenced by Next Generation Sequencing

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<tr>
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<td>MPL</td>
<td>WT1</td>
</tr>
<tr>
<td>GATA1</td>
<td>NOTCH1</td>
<td>ZRSR2</td>
</tr>
</tbody>
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Figure 1. First Marrow Biopsy showing hypocellular bone marrow mostly composed of myeloid cells.

Figure 2. High powered view of first marrow biopsy showing paucity of megakaryocytes and one multinucleated dysmorphic megakaryocyte slightly favoring MDS over AA.
Discussion
Modern molecular genetics has dramatically advanced our understanding of MDS. Dozens of MDS-associated genes have been identified since the publication of the 2008 WHO guidelines. However, its use in the clinical setting has been unclear. Currently, diagnosis of MDS hinges on morphologic assessment, which relies on subjectively assessing for dysplasia and quantification of blast forms. This contributes to diagnostic uncertainty and error in morphologically similar processes that cannot be ruled out such as nutrition deficiencies, toxin exposures, other myeloid neoplasms, h-MDS and AA. Recent studies identified at least one MDS-related mutation in 50% of suspected MDS cases that failed to meet morphologic criteria. When morphologic assessment cannot diagnose MDS then cytogenetic tests are utilized to help distinguish MDS from other processes that may mimic MDS, however it is well documented that there are cases of MDS without blasts or chromosomal abnormalities on karyotype as presented in our case. When morphologic assessment fails to differentiate a patient with h-MDS versus AA, then molecular genetic techniques should be considered to aid in the diagnosis.

Next-generation sequencing will undoubtedly become a part of routine MDS care and opens the door for possible targeted therapies and agents to avoid during therapy. It has already been demonstrated that MDS patients with TP53 mutations and del(5q) have poor responses to lenalidomide therapy. It was also found that patients with TP53 mutations have increased risk of mortality and relapse after Hematopoietic Stem Cell Transplantation. Our case is an example of next-generation sequencing as a powerful diagnostic, prognostic, and therapeutic planning tool in the management of a patient with h-MDS. Treatment with Immunosuppressive therapy and supportive therapy with hematopoietic growth factors were initiated based on this patient’s MDS mutations.

Conclusion
The differentiation of AA and h-MDS using mainstream histopathologic evaluation and cytogenetic studies alone is difficult, prone to interobserver variability and error. Next generation gene sequencing for MDS/AML associated mutations may significantly improve diagnostic accuracy and should be considered when diagnosis remains unclear after standard evaluation.

Disclaimer
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Conflict of Interest
All of the above authors have no financial disclosures or conflicts of interests related to this study.

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References
Chewing the Fat: A Case Report of Therapeutic Plasma Exchange in Hypertriglyceridemia-Induced Pancreatitis

Cory Madigan MD; Troy Denunzio DO; and Jessica Bunin MD

Abstract
Hypertriglyceridemia is the third most common etiology of acute pancreatitis, but lacks a clear, evidence-based treatment approach. We present the case of a 25-year-old man who was admitted eleven times over seven years for hypertriglyceridemia-induced pancreatitis. In his first ten admissions, he received conservative therapy. During his eleventh admission, he underwent therapeutic plasma exchange with lowering of serum triglycerides from 5080 to 332 mg/dL. He was discharged on hospital day five and was noted to have persistently lowered triglyceride levels upon follow up. The case affirms plasma exchange’s ability to rapidly lower serum triglyceride levels and provides future research opportunities for examining the long-term effects of this treatment.

Keywords
acute pancreatitis, hypertriglyceridemic pancreatitis, severe hypertriglyceridemia, therapeutic plasma exchange

Introduction
Hypertriglyceridemia is thought to be the underlying etiology of 1%-4% of cases of acute pancreatitis (AP). It is currently postulated that pancreatic toxicity is caused by fatty acid metabolites of triglycerides. Despite being the third most common cause of AP, the American College of Gastroenterology guidelines on the management of pancreatitis do not specifically provide a treatment approach for AP caused by severe hypertriglyceridemia. Historically, treatment has largely been supportive, although many have examined specific therapies that target serum triglyceride levels. The three most commonly utilized of these therapies include intravenous insulin, intravenous heparin, and therapeutic plasma exchange (TPE). TPE has been shown to rapidly lower serum triglyceride levels and has been retrospectively analyzed as having a potential treatment role in hypertriglyceridemia-induced pancreatitis (HIP). In this case report, we examine the case of a young man admitted eleven times for HIP over the course of seven years who underwent TPE on his last admission.

Case Presentation
We present the case of a 25-year-old man with history of familial hypertriglyceridemia, hypertension, obstructive sleep apnea, and morbid obesity with a total of eleven admissions for what was ultimately determined to be HIP. His medications at the time of his last admission included atorvastatin, niacin, fenofibrate, fish oils, aspirin, and losartan. Over the course of his previous admissions, he was evaluated for common causes of AP, but denied the use of alcohol and had multiple imaging studies, including magnetic resonance cholangiopancreatography, which did not show evidence of cholelithiasis or other biliary disease. Of primary interest, the patient’s average serum triglyceride level at presentation for each of his episodes was 2325 mg/dL with standard deviation of 1580 mg/dL. His outpatient and inpatient serum triglyceride levels versus time are displayed in Figure 1. His presentations were characterized by average Bedside Index for Severity of Acute Pancreatitis (BISAP) scores of 0.8±0.8 and average length of stay of 3.7±1.4 days. Other average laboratory values and data are included in Table 1.

During the patient’s first ten admissions, he was treated with supportive care consisting of intravenous fluids, analgesia, and bowel rest. In the patient’s eleventh admission, he developed oliguric acute kidney injury (AKI) and was transferred to the intensive care unit (ICU) for further management. In the ICU, he underwent two 0.5-volume exchange sessions of TPE with 5% albumin, with lowering of serum triglycerides from 5080 to a nadir of 332, a reduction of 93%. He was discharged in stable condition with resolution of his symptoms and AKI. At his first follow up visit, the patient’s serum triglyceride value was 568 mg/dL, his lowest outpatient value over a ten year period.

Discussion
The potential role of TPE in HIP is not well validated by large prospective studies. The 2013 Guidelines on the Use of Therapeutic Apheresis discuss the potential role of plasma exchange for HIP and give it a 2C recommendation, meaning only weak observational data is currently available. Nevertheless, a growing body of retrospective and observational literature over the past few years reports good outcomes with TPE’s use. A 2015 systematic review of 74 case reports and case series found that the average percent reduction was over 85%. In this same study, the overall mortality of all patients included in the analysis was 7.1%. Unfortunately, due to the retrospective and anecdotal nature of these analyses, drawing conclusions about the effect of TPE on mortality is not possible due to inherent patient selection and publication biases. Nevertheless, TPE is garnering more attention due to its ability to rapidly lower serum triglycerides, which are felt to be pathogenic. Furthermore, TPE is relatively safe. In a recent case series of thirteen patients who underwent TPE for HIP, there were no complications attributed to TPE. Thus, while many questions remain, TPE is a reasonable consideration when treating HIP.

This case report highlights several important points regarding the role of TPE in HIP. Firstly, it shows the efficacy of TPE as a mechanism to lower serum triglyceride levels. Secondly, it emphasizes the need to bring broader recognition of TPE as a viable treatment option for moderate to severe pancreatitis. Upon
Figure 1. The blue circles represent the patient’s inpatient and outpatient serum triglyceride levels from March, 2008 through April, 2016. Admissions for AP are marked by red squares. Treatment with TPE is marked by green triangles.

Table 1. Clinical and laboratory values from his eleven admissions. The second column includes averages and standard deviation.

<table>
<thead>
<tr>
<th>Hospitalization Data at Presentation</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days Hospitalized</td>
<td>3.7 ± 1.4</td>
</tr>
<tr>
<td>BISAP score</td>
<td>0.8 ± 0.8</td>
</tr>
<tr>
<td>SIRS Criteria</td>
<td>1.7 ± 0.9</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>97.5 ± 13.4</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>19.6 ± 3</td>
</tr>
<tr>
<td>Temperature (F)</td>
<td>98.6 ± 1.1</td>
</tr>
<tr>
<td>Lipase (Units/L)</td>
<td>1061.8 ± 2334.2</td>
</tr>
<tr>
<td>Amylase (Units/L)</td>
<td>92.8 ± 24.4</td>
</tr>
<tr>
<td>Serum Triglycerides (mg/dL)</td>
<td>2325.3 ± 1580.2</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>118.5 ± 33.9</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>22.8 ± 5.3</td>
</tr>
<tr>
<td>WBC (per microliter)</td>
<td>13.6 ± 2</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>41.7 ± 1.5</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>133.1 ± 3.7</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>9.7 ± 2.8</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.3 ± 0.5</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>98.3 ± 9.3</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (Units/L)</td>
<td>676.3 ± 267.3</td>
</tr>
<tr>
<td>Aspartate Aminotransferase (Units/L)</td>
<td>38.3 ± 12.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>128.6 ± 11</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>41 ± 3.5</td>
</tr>
</tbody>
</table>

Figure 2. Representative, “Crisco®-like” blood-draw of a patient with severely elevated triglycerides.
diagnosis, prompt transfer to the ICU should be considered. This is of special importance to military and family practitioners as patients with familial hypertriglycemia often present in young adulthood. Thirdly, the report acts as a foundation for further research by the authors to compare outcomes of HIP who received TPE vs those who did not. Lastly, given this patient’s numerous admissions, this report raises a possible role for TPE in preventing readmission, long-term sequelae of pancreatitis, and other morbidities associated with the disease.

Conclusion
HIP is a relatively common illness that often first presents in young adults. There is currently no consensus on TPE’s role in improving measurable outcomes in HIP, but it is a consistent method to rapidly lower the serum triglyceride level. Its use for acute pancreatitis due to severe hypertriglyceridemia should be considered in any patient with moderate to severe pancreatitis with elevated triglycerides.

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Conflict of Interest
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References
DaT’s Awesome: Hawai‘i’s First Dopamine Transporter (DaT) Nuclear Medicine Study

Eric J. Royston DO, MPH; Yang-En Kao MD; and Kevin M. Nakamura MD

Abstract

Parkinsonian Syndromes are difficult to accurately diagnose and distinguish from other neurological processes such as essential tremor. Until now, physical exam and clinical presentation have been the gold standard for diagnosis (bradykinesia, tremor, rigidity, and postural instability). However, this leads to over- or under diagnosis and improper treatment due to variability in presentation and symptoms.

A nuclear medicine study using I-123 Ioflupane (DaTSCAN) has been developed, which allows accurate differentiation of Parkinsonian Syndromes from other etiologies. This study is now widely performed on the mainland, but has never been done in Hawai‘i due to its East Coast sourcing and relatively short physical half-life. Through a highly coordinated logistical effort, Tripler Army Medical Center’s Nuclear Medicine Department conducted the first DaTSCAN in Hawai‘i in April 2016.

Keywords
DaTscan; parkinsonian syndrome

Introduction

I-123 is a radionuclide that is produced in a cyclotron. It has a relatively short half-life of 13.2 hours. It is widely used in nuclear medicine with single photon emission computed tomography (SPECT) imaging. Ioflupane is a phenyltropane compound which is a derivative of cocaine. It has a high affinity for presynaptic dopamine receptors which have a predominante abundance in the striatal region – which is the region most affected by Parkinsonian Syndromes.

The combined I-123 Ioflupane is a radiopharmaceutical that takes the imaging characteristics of I-123 and the dopamine receptor affinity of Ioflupane and allows for excellent imaging abilities of Parkinsonian syndromes. DaTSCAN is produced on the East Coast; its short half-life has prevented any prior studies to be performed in Hawai‘i.

Case Presentation

A 21-year-old man presented to his neurologist with intermittent right upper extremity tremors, which interfered with his shooting range performance. Neurological exam demonstrated resting and postural tremors. Additionally, mild bradykinesia was noted in the left hand. Upon walking, the tremors persisted and there was decreased arm swing.

Based on the physical exam findings, the clinician suspected Parkinson’s Disease. Following a normal brain MRI and lab work, a DaTSCAN was requested to confirm or exclude the clinical diagnosis of Parkinson’s Disease. The DaTSCAN study was normal and the patient was diagnosed with essential tremor.

Discussion

Parkinsonian Syndromes (including Parkinson’s Disease, Progressive Supranuclear Palsy, and Multisystem Atrophy) are one of the most common neurodegenerative disorders.

In Parkinsonian Syndromes, the quantity of dopamine transporters in the striatum are decreased by approximately 50%-70%. SPECT imaging is performed to capture the gamma energy produced by I-123 Ioflupane (159 keV), to quantitate the amount of dopamine transporters. When the quantity is decreased, less uptake is demonstrated, allowing for the diagnosis of Parkinsonian Syndrome.

I-123 Ioflupane allows for a specific imaging modality for Parkinsonian syndromes with an earlier detection method than MRI, which is not as specific.

One limitation to the DaTScan is that it cannot distinguish between the different types of Parkinsonian syndromes. However, the ability to diagnose the class of disorders is paramount.

Conclusion

TAMC performed the first DaTSCAN in Hawai‘i, and demonstrated the feasibility of locally confirming or ruling out Parkinsonian Syndromes. This pioneering achievement will improve care for our military beneficiaries and pave the way for civilian clinicians as well. The ability to make an earlier diagnosis may lead to better treatments and outcomes.
Figure 1. SPECT imaging demonstrating a normal distribution in the caudate nuclei and the putamen (striatal region) as evidenced by the increased radiotracer uptake in this 21-year-old man.
**Disclaimer**
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**Conflict of Interest**
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**References**
Benign Granuloma Masquerading as Squamous Cell Carcinoma Due to a “Floater”

Phalagoon A. Shah MBBS; Madeleine P. Prat MD; and David C. Hostler MD, MPH

Abstract
Pathology specimen cross-contamination is a rare phenomenon in diagnostic pathology. Such “floaters” may result in delayed, missed or erroneous diagnoses. We describe the case of a patient with benign granuloma of the lung initially misdiagnosed as squamous cell carcinoma due to a “floater.”

Keywords
humans; pathology, surgical/standards, granuloma

Introduction
In diagnostic pathology, tissue fragments are encountered that are morphologically dissimilar to the main specimen. These contaminants or extraneous tissues are called “floaters.” This occurs as a result of carrying over tissue pieces from one case to another during specimen processing. The exact incidence of floaters in anatomic pathology is uncertain. However it has been estimated, depending on the study method, to be between 0.6% and 2.9%.1 The presence of floaters can have serious consequences, including delaying diagnosis or misdiagnosing patients. Herein we describe the case of a patient with a benign granuloma of the lung initially misdiagnosed as squamous cell carcinoma due to a “floater.”

Case Presentation
A 68-year-old man with a 50 pack-year smoking history and prior exposure to Agent Orange was referred to the pulmonary clinic for exertional dyspnea. CT Chest revealed a 1.1 cm spiculated right upper lobe nodule and mediastinal lymphadenopathy (Figures 1, 2). PET-CT demonstrated abnormal uptake in the nodule and mediastinal lymph nodes (Figure 3). Endobronchial ultrasound-guided transbronchial needle aspiration biopsy of the right paratracheal lymph node was obtained. Cytopathology identified a small cluster of atypical cells with an immunohistochemical stain profile consistent with squamous cell carcinoma of the lung (Figures 4, 5), yielding an initial diagnosis of cT1aN2M0 (Stage IIIa) lung cancer (Table 1). Multidisciplinary review at tumor board raised concern that the cells were morphologically inconsistent with squamous cell carcinoma and N2 disease was incongruous with the putative primary lesion. Cervical mediastinoscopy was performed; all lymph nodes were benign. The nodule was resected by video assisted thoracic surgery wedge resection; final pathology indicated an old granuloma due to an endemic fungal pathogen (Figure 6).

Discussion
Floaters may be introduced during specimen grossing, embedding, sectioning, or histological staining. However there is no consensus as to which specific step of specimen processing is to blame for the introduction of extraneous tissue. Gephardt, et al, reported that their tissue contamination frequency was higher in paraffin blocks than it was in slides.2 In contrast, Layfield, et al, found that the histology laboratory was the origin of most contaminants either during the section cutting process or the staining process.3 Their water baths were also contaminated by minute fragments of tissue remaining from the cutting of prior specimens. Platt, et al, found a high number of contaminants in the staining baths, with approximately 26 tissue fragments per bath.4

When these floaters consist of cancerous tissue, it can result in a false positive diagnosis, but also incorrect cancer staging, whether higher or lower. Up to 30% of these contaminants consisted of either abnormal tissue or cancerous cells5 The recognition of a tissue sample as a floater is not always straightforward. It is easy to identify an error when the observed tissue is completely contrary to what one might expect eg, prostate tissue in an endometrial sample.3 However, interpretation becomes more difficult when the floater has the same tissue type or is a significant lesion. One of the most challenging contexts, when dealing with a possible floater occurs when the diagnostic tissue has neoplastic cells that cannot be ignored nor can it be declared as a malignancy with 100% confidence. When necessary, molecular testing can be used to establish identity of the tissue, but molecular testing is time-consuming and expensive, and repeat biopsy exposes the patient to additional procedure-related risks.

This data suggests that true diagnostic challenges due to slide contaminants are relatively rare. However, one must consider that in the era of minimally-invasive diagnostic techniques and small sample sizes, interpreting or identifying contamination has become even more challenging. Floaters are confounding even with surgical biopsies measured in centimeters. It is significantly more difficult to distinguish true sample from potential floater if the sample, in its totality, is small and hypo-cellular. As many specialists, including pulmonologists, continue to push the boundaries of minimally-invasive diagnostics, we must recognize the limitations of our techniques. In this case, it was the collective clinical intuition of thoracic specialists which questioned the sample results and prevented the inappropriate and potentially harmful administration of induction chemoradiation therapy.

Considering the consequences of evaluating contaminated slides and the risk of misdiagnosis, preventative measures should be taken in the pathology laboratory. Cleaning of the
Figure 1. CT coronal cut, lung window, showing right upper lobe nodule

Figure 2. CT axial cut, body window, showing 4R lymph node

Figure 3. Fused PET CT, axial cut, showing 4R lymph node

Figure 4. TBNA of right paratracheal lymph node, H&E, 400x, demonstrating predominantly lymphocytes, with rare admixed epithelioid cells

Figure 5. TBNA of right paratracheal lymph node, CK5/6, 400x, demonstrating the rare epithelioid cells are reactive with CK5/6

Figure 6. Wedge resection of right upper lobe nodule; Gomori-methamine-silver stain; 600x; demonstrating numerous small (4-6 microns), mildly pleomorphic yeast forms with focal grooving and narrow based budding
Table 1. Stage groups according to TNM descriptor and subgroups

<table>
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<th>T/M</th>
<th>Subgroup</th>
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<th>N1</th>
<th>N2</th>
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<td>T1a</td>
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<td>IIa</td>
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<td>T3</td>
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<tr>
<td></td>
<td>M1a PI Disem</td>
<td>IV</td>
<td>IV</td>
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</table>

Water bath and frequent changing of the water will prevent the transmission of contaminants to subsequent sections. Newer staining systems can also be used, that do not use shared baths. As far as contamination at the grossing station is concerned, having a clean technique and being organized seems to be the best approach to prevent errors. Finally, in addition to process improvement, clinicians should be aware of pathology specimen cross-contamination when interpreting biopsy results, especially with small samples in the era of minimally-invasive diagnostics. If results do not fit the clinical picture, a healthy dose of skepticism can protect patients from significant harm.

Conclusion
Clinicians should be aware of pathology specimen cross-contamination when interpreting biopsy results, especially with small samples in the era of minimally-invasive diagnostics. If results do not fit the clinical picture, a healthy dose of skepticism can protect patients from significant harm.

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Conflict of Interest
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