

## **Disseminated Histoplasmosis: A Case of Pancytopenia in an AIDS Patient**

Stephen Malutich, Vikesh Khanijow MD, Kevin Chap MD, Ramal Weragoda MD PhD.

### **Introduction:**

Histoplasmosis is one of the most common pulmonary and systemic mycoses occurring in the United States, caused by the dimorphic fungus *Histoplasma capsulatum*. Although found throughout the world, it is ubiquitous in the Ohio, Missouri, and Mississippi River valleys. The mycelial form is found in large concentrations in soil contaminated by the droppings of infected bats and birds, and in these endemic areas *H. capsulatum* skin test positivity is as high as 90%<sup>1</sup>. An estimated 40 million people living in the United States have been infected with *H. capsulatum*, and approximately 500,000 new cases occur each year. We report a case of a 39 year old woman presenting with classic symptoms of disseminated histoplasmosis<sup>2</sup>.

### **Case Presentation:**

This is a case of a 39 year-old Caucasian woman with a past medical history of AIDS with last CD4 count of 12 cells/ $\mu$ L and viral load of 7.1 million copies/mL, hepatitis C, history of miliary tuberculosis treated with eleven month course of isoniazid and rifampin, and history of treated *Pneumocystis jirovecii* pneumonia (PCP), presenting with a three week history of fever to 103°F, productive cough with clear sputum, fatigue, and weight loss of 25 pounds over the past month. Upon initial presentation she was found to be cachectic, with poor dentition and diffuse muscle wasting. No hepatosplenomegaly or clinical signs of hypoxia were appreciated. Initial chest x-ray (see Figure 1a and 1b) showed ill-defined reticulonodular airspace opacities bilaterally. The preliminary differential diagnoses included PCP pneumonia, tuberculosis, community-acquired pneumonia, legionella, histoplasmosis, and *Mycobacterium avium*-complex infection. Her initial complete blood count was leukopenic and anemic with a white blood cell count 2700 cells/mL, hemoglobin 7.9 g/dL, hematocrit 22.0% and platelet count 152,000 cells/mL. Her lactate dehydrogenase level was 4,707 IU/L. These values fortified the suspicion for PCP or histoplasmosis, and also raised concern for cytomegalovirus, Epstein-Barr virus, and parvovirus B19 infections. Broad spectrum antibiotic therapy was initiated with cefepime, vancomycin and sulfamethoxazole/trimethoprim, but no clinical improvement was observed. Acid-fast smears for tuberculosis and bacterial cultures were negative and the suspicion of fungal etiology was increased. The patient underwent a bone marrow biopsy to investigate her progressive pancytopenia, which revealed hypocellular marrow with *Histoplasma capsulatum* organisms noted in the histiocytes' cytoplasm (see Figure 2). Treatment with amphotericin B was begun and after showing marked clinical improvement, the patient was discharged on oral itraconazole.

### **Discussion:**

Primary histoplasmosis infection typically occurs from alveolar deposition of spores from disturbed soil, but can also occur from a reactivated latent focus of infection. Once it enters the body, the organism grows into its yeast form, which is not transmissible through person-to-person contact. Patients with evidence of previous *H.*

*capsulatum* exposure can be up to twice as likely to develop symptomatic disease compared to previously unexposed patients; however, the overall risk of reactivation without repeat exposure is low<sup>3</sup>. In immunocompetent patients, up to 90% of infections will be asymptomatic and only 20% of symptomatic infections will require treatment<sup>4</sup>. The most severe cases occur in immunocompromised hosts, and approximately 55% of HIV-infected patients will progress to symptomatic disease that often becomes disseminated in nature<sup>5</sup>.

The presentation of disseminated histoplasmosis typically occurs in immunocompromised patients or in the elderly. Clinical signs include cough, fever, fatigue, night sweats, weight loss, anorexia, and respiratory symptoms<sup>6</sup>. Hepatomegaly, splenomegaly, and bone marrow suppression with significant pancytopenia from fungal invasion may be present. In many cases, the only findings may be progressive fever and weight loss. Markedly elevated ferritin, alkaline phosphatase<sup>7</sup>, and lactate dehydrogenase levels<sup>1</sup> have been shown to be associated with disseminated infection, but are relatively nonspecific. Chest radiographs typically reveal lower lobe interstitial or reticulonodular infiltrates.

There are multiple approaches of achieving the diagnosis of histoplasmosis, but the sensitivity of the available methods is dependent on the degree of fungal burden. Cultured *H. capsulatum* from any body fluid provides the strongest evidence for active infection; however, cultures may take up to 4 weeks to become positive in patients with new infections. The sensitivity of sputum culture in acute pulmonary infection is only 15% as compared to 60-85% in chronic infections, and the sensitivity of blood cultures in progressive disseminated histoplasmosis only reaches 50-70%<sup>9</sup>. In patients that have a high clinical suspicion for histoplasmosis, antigen testing may be a more useful clinical tool. The sensitivity of urine antigen testing in patients with high fungal burden is 80-95%, and results can be obtained within 48 hours in most cases<sup>7</sup>. Patients with disseminated disease with bone marrow invasion can also be diagnosed with bone marrow biopsy. In 75% these cases, intra- or extracellular *H. capsulatum* organisms can be visualized with appropriate fungal stain<sup>10</sup>.

The treatment for histoplasmosis is tailored to the severity of the infection and involves therapy with amphotericin B, itraconazole, or a combination of the two. For patients with severe acute pulmonary histoplasmosis, amphotericin B is indicated. Itraconazole may be used for milder infections. The duration of therapy is not well established, but treatment for 3 months is considered reasonable<sup>11</sup>. For chronic pulmonary cases, amphotericin B is indicated until clinical response is noted, at which time switching to oral itraconazole is appropriate. The risk of relapse is high in chronic pulmonary cases (10-25%) and the duration of treatment should be at least 1 year<sup>12</sup>. In cases of progressive disseminated disease, liposomal amphotericin B has been shown to be more effective than the standard formulation in treating AIDS patients<sup>13</sup>. Once clinical response is observed, further therapy may be changed to itraconazole for one year until clinical findings resolve<sup>14</sup>. Antigen urine testing can be used to monitor remission and should be negative before discontinuation of therapy.

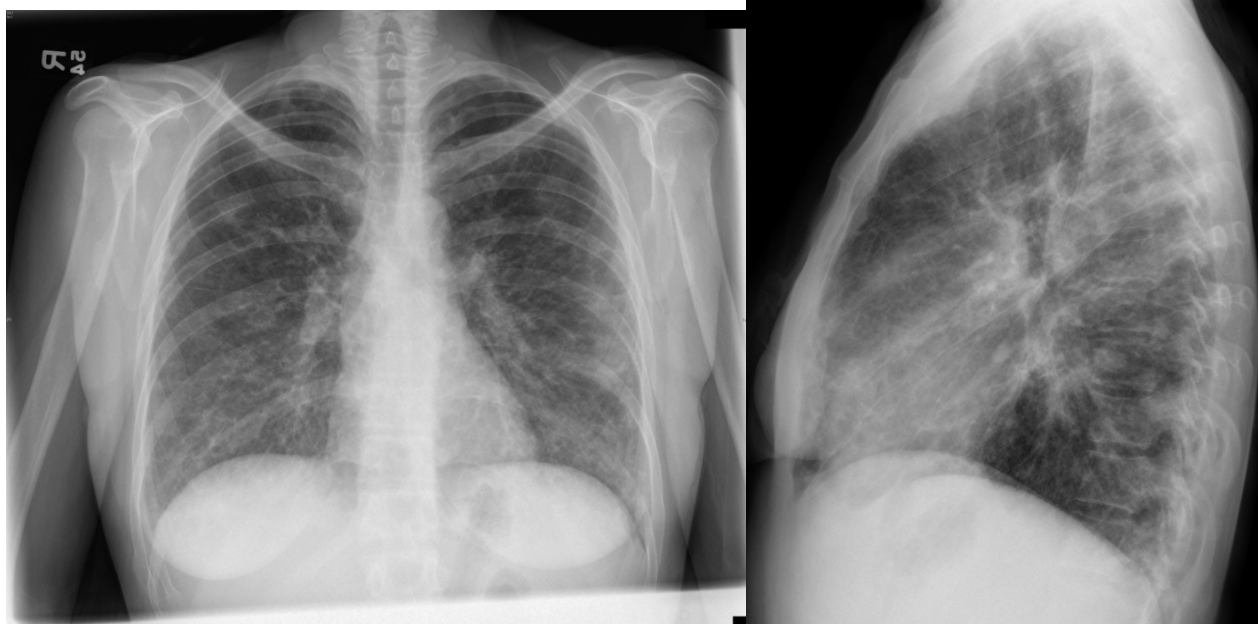
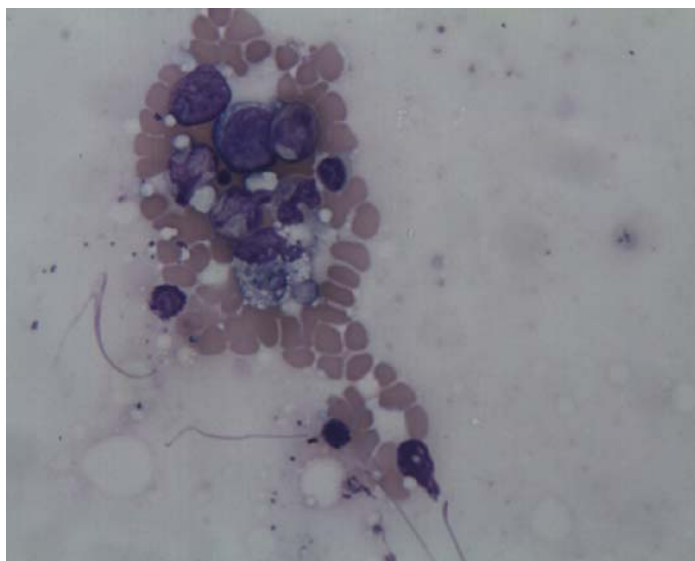


Figure 1: PA (1a) and lateral (1b) plain radiographs demonstrating bilateral reticulonodular airspace opacities.



### Conclusions:

Infection with *H. capsulatum* is an important diagnosis to consider in patients with progressive pulmonary symptoms, especially in those that are immunocompromised and not responding to antibiotic regimens. It is important to remember that histoplasmosis may present with vague, nonspecific symptoms, most commonly only fever and weight loss. Those with significant disease should be administered amphotericin B and transitioned to itraconazole when clinically improving.

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## **Fever in a patient after Transarterial Chemoembolization (TACE)**

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### **Introduction:**

TACE is an effective treatment for advanced liver cancer and unresectable hepatocellular carcinoma. However, like any procedure, it has multiple potential complications. Post-embolization syndrome is common amongst patients who undergo TACE, but is many times difficult to differentiate from other post-procedure complications.

### **Case Presentation:**

A 52 year old white man with hypertension (HTN), gastroesophageal reflux disease (GERD), hepatitis C cirrhosis, hepatocellular carcinoma (HCC) status post transarterial chemoembolization (TACE) in 3/10 and radiofrequency ablation (RFA) in 4/10 presented with fevers of three days duration and right upper quadrant pain of one week duration following repeat TACE one week ago for residual HCC. The highest temperature recorded at home was 102.5 F. Fevers are associated with chills, rigors and generalized fatigue. He denies cough, shortness of breath, chest pain, diarrhea, jaundice, dysuria, rash, and headaches. No history of trauma, recent travel, or sick contacts. He has no known drug allergies and he takes esomeprazole for GERD, hydrochlorothiazide and valsartan for HTN. He denies current illicit drug use, smoking or alcohol intake. He underwent tonsillectomy in 1970 and cholecystectomy in 2006.

On exam, his oral temperature was 98.7 F, pulse rate was 76 beats per minute, blood pressure was 122/78 mm Hg and respiratory rate was 20 breaths per minute. Physical examination was negative for any sign of infection (no consolidation, crackles, cardiac murmur, abdominal tenderness, hepatomegaly, ascites, rash, conjunctivitis, sinusitis, joint effusion). Laboratory work up revealed ALT 129, AST 127, ALP 78, total bilirubin 0.9, WBC 9.6 with 75% neutrophils, 18% lymphocytes and 7% monocytes, INR 0.91, and a normal urine analysis and microscopy. Chest X ray was normal. He was started on vancomycin, cefepime, and metronidazole because of a suspicion of infection after blood and urine cultures were drawn. A CT scan abdomen and pelvis with and without contrast showed post embolization changes without any evidence of abscess formation. During the hospitalization, he was persistently febrile but his abdominal pain resolved and his liver enzymes decreased

(ALT 109 and AST 96). Blood and urine cultures were negative. Thus, he was discharged to home with a 10 day course of ciprofloxacin with a diagnosis of post-embolization syndrome.

## **Discussion:**

After TACE, nearly 18-67% of patients develop fever in association with any or none of the following-nausea, vomiting, and right upper quadrant abdominal pain<sup>1</sup>. This symptom complex is referred to as “post-embolization syndrome”. These symptoms can last up to 1-2 weeks. Most of the post-TACE fever peaks within the first 2 days after TACE (in 97% of patients)<sup>1</sup>. In this syndrome, fever is always associated with liver enzyme abnormalities<sup>4</sup>.

The pathogenesis of post-embolization syndrome is multifactorial:

1. Embolism can lead to necrosis of normal hepatocytes.
2. Chemotherapeutic drugs have their own toxicities.
3. The procedure itself can lead to release of inflammatory factors.
4. Normal stress response<sup>6</sup>.

In a study by Li *et al.*, patients who developed fever were of younger age, had larger tumor size, had higher doses of medicines administered, and had a higher embolized volume. Multivariate analysis showed that tumor size > 3 cm and a total dose of > 33 are the most independent predictive factors of post-TACE fever<sup>3</sup>.

Earlier, it was thought that occurrence of fever is a good prognostic marker as the fever is believed to be the result of tumor necrosis<sup>4,5</sup>. However, based on studies by Paye, *et al.* and Wigmore, *et al.*, fever is proven to reflect an injury to the non tumorous liver parenchyma and not tumor necrosis. It is also shown that post-embolization syndrome is associated with an adverse outcome which goes along with the above inference<sup>5</sup>.

However, the clinical dilemma is how to differentiate post-embolization fever from liver abscess after TACE as both can present with the same symptoms. Basing on Ong *et al.* study, the incidence of post-TACE liver abscess is 0.26% with a mortality of 40%<sup>3</sup>. Thus, it is very important to differentiate post-TACE fever from liver abscess because the management is completely different. But, there are no single criteria or constellation of clinical features which can contrast the two. The authors noted that the most common symptom of a post-TACE liver abscess is fever which is seen in 92% of subjects. Among the patients with a liver abscess who developed fever, nearly 90% had recurrence of fever at least 3 days after resolution of post-TACE fever<sup>3</sup>. In the past, most common organisms isolated were Gram positive bacteria. Currently, Gram negative bacteria are identified more often; most commonly, the organisms are *Escherichia coli*, *Citrobacter*, and *Proteus mirabilis*, but often are polymicrobial. Blood cultures are positive in only 40% of such patients<sup>3</sup>. Thus, even though the probability of our patient’s fever coming from a liver abscess is highly unlikely, because of the low yield of blood cultures as well as the high mortality associated with a liver abscess, we started the patient on broad spectrum antibiotic coverage (vancomycin for Gram positive organisms, cefepime for Gram negative organisms, and metronidazole for anerobes) and switched to oral ciprofloxacin once all the cultures were negative because of the difficulty to differentiate post-embolization changes from early abscess formation even on a CT scan .

## **Conclusions:**

Fever is a common symptom following TACE. A diagnostic dilemma exists since symptoms, blood cultures and CT scans may not help differentiate post-embolization syndrome from a liver abscess. These patients, therefore, require close monitoring and antibiotics when appropriate.

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## **Normal Pressure Hydrocephalus or Binswanger Disease? You be the judge.**

Justin Rice MD.

## **Introduction:**

Normal Pressure Hydrocephalus (NPH) is a potentially treatable cause of dementia characterized clinically by the classic triad of dementia, urinary incontinence, and gait ataxia/apraxia. A more rare disorder, Binswanger disease, shares many clinical and diagnostic similarities with NPH. I present a case of presumed Binswanger disease to demonstrate the diagnostic dilemmas that may arise in a patient with dementia, urinary incontinence, and gait ataxia.

## **Case Presentation:**

A 76 year old Latin American woman with a past medical history of long-standing diabetes mellitus, chronic hypertension, and a subacute left thalamic stroke presented to the emergency department with several months of progressively diminishing mental and functional status. The patient lives with and is cared for by her daughter.

Seven months prior to presentation, the patient's family had noticed increased clumsiness and frequent falls due to an unsteady gait described as her feet "glued to the floor." They also noted increased forgetfulness, slowness of thoughts and speech, as well as frequent irritability worsening over the same time period. The daughter mentions the patient has been intermittently incontinent of urine and recently has become completely reliant on adult diapers. Due to the progressive nature of her symptoms, the patient has spent most of her time in bed with subsequent deconditioning and poor oral intake.

On physical examination, vital signs were within normal limits with the exception of an elevated blood pressure at 158/92. Pertinent physical exam findings were a cachectic appearance, stage one decubitus ulcers on bilateral heels and lower sacrum, and a skin rash involving the bilateral inguinal regions and perineum. Neurologically, the patient was oriented to name and location only. There were no focal neurologic deficits; however, she was slow to follow commands. Her Mini-Mental Status Exam score was 18 out of 30.

Complete blood count and complete metabolic profiles were normal, as well as a urinalysis, urine drug screen, TSH, and Vitamin B12 level. RPR was nonreactive. Lumbar puncture showed an opening pressure of 13 cmH<sub>2</sub>O, closing pressure of 11 cmH<sub>2</sub>O, negative CSF VDRL, and negative CSF gram stain/culture. The appearance and cell count of the CSF are shown below:

Appearance	Clear
RBC	1
WBC	<1
Glucose, CSF	58
T Protein, CSF	68.2

Of note, there was no improvement in symptoms after approximately 45 ml of CSF was removed.

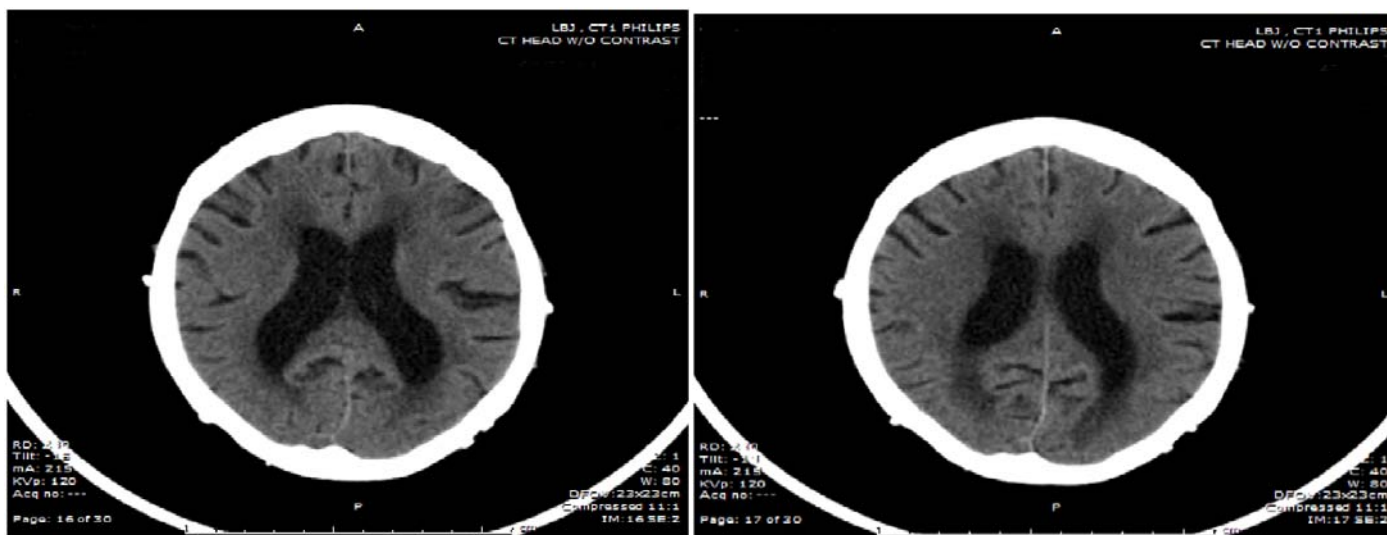


Figure 1a & 1b: CT scan of brain without contrast revealed enlarged ventricles out of proportion to sulcal atrophy and a left, subacute thalamic stroke.

Over the course of the hospitalization, the diagnosis of NPH was considered based on the clinical symptoms at presentation, normal CSF studies and opening pressure, and radiologic findings. It was noted, however, that in the absence of more sophisticated neuroimaging techniques needed to examine CSF flow dynamics, the diagnosis of Binswanger disease could not be ruled out, and, in fact, was the more likely diagnosis given the patient's medical history and recent thalamic stroke.

**Discussion:**

Binswanger disease, also known as chronic progressive subcortical encephalopathy, is a rare condition in which infarction of the subcortical white matter occurs subacutely. The pathophysiologic basis of the disease is not completely clear, but it typically occurs in older patients with severe, long-standing hypertension or diabetes mellitus.<sup>1</sup> It has long been recognized that both NPH and Binswanger disease can present with the triad of gait disturbance, dementia, and urinary incontinence.<sup>2</sup> Furthermore, diagnostic modalities including CT and MRI imaging along with CSF studies may provide little delineation between the two entities.

*Table 1<sup>1,3,4,5</sup>*

Binswanger Disease	Normal Pressure Hydrocephalus
<b>Clinical Manifestations:</b> <ul style="list-style-type: none"> <li>• Unsteady, broad-based gait</li> <li>• Urinary symptoms not caused by urologic disease</li> <li>• Subcortical dementia with deficits in executive function</li> </ul>	<b>Clinical Manifestations:</b> <ul style="list-style-type: none"> <li>• Magnetic broad-based gait, progressive in nature</li> <li>• Urinary frequency, urgency, or frank incontinence</li> <li>• Dementia with diminished frontal and subcortical deficits</li> </ul>
<b>CSF Studies:</b> <ul style="list-style-type: none"> <li>• Opening pressure normal</li> <li>• Normal cell count and differential</li> <li>• Normal protein</li> <li>• Normal glucose</li> </ul>	<b>CSF Studies:</b> <ul style="list-style-type: none"> <li>• Opening pressure normal to high-normal</li> <li>• Normal cell count and differential</li> <li>• Normal protein</li> <li>• Normal glucose</li> <li>• May show clinical improvement after removing &gt;30cc of CSF</li> </ul>
<b>CT/MRI Findings:</b> <ul style="list-style-type: none"> <li>• Ventricular enlargement due to periventricular ischemic demyelination</li> <li>• Hyperintensity involving periventricular white matter</li> <li>• Accompanying lacunar infarcts</li> </ul>	<b>CT/MRI Findings:</b> <ul style="list-style-type: none"> <li>• Ventricular enlargement due to periventricular edema</li> <li>• Prominent periventricular hyperintensity</li> <li>• Periventricular edema</li> </ul>

<p>Treatment:</p> <ul style="list-style-type: none"><li>• Supportive, risk factor reduction</li></ul>	<p>Treatment:</p> <ul style="list-style-type: none"><li>• Approximately 30 to 50% of patients identified as having NPH will show improvement with a ventricular shunting procedure</li><li>• Gait may improve more than memory</li></ul>
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### **Conclusion:**

The differential diagnosis of NPH includes Binswanger disease, which causes ventricular dilation, similar CSF findings, and presents with the same clinical triad. In the absence of more advanced neuroimaging techniques, a conclusive diagnosis may remain elusive. However, differentiating between the two diseases may have important treatment implications in certain clinical scenarios. Further research is needed to discern if failure of treatment of NPH with ventricular shunting is due to ineffectiveness of the procedure itself or incorrect diagnosis.

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## **Asymptomatic Anemia with a History of Autoimmune Disease**

Chad Hruska MS III, Bao T. Nguyen DO, PhD.

### **Introduction:**

Anemia is the most common disorder of the blood. It is the primary cause of 5.5 million outpatient visits annually and is attributed to a variety of causes<sup>1</sup>. The following case report highlights a less common etiology of anemia in a patient with a history of autoimmune disease.

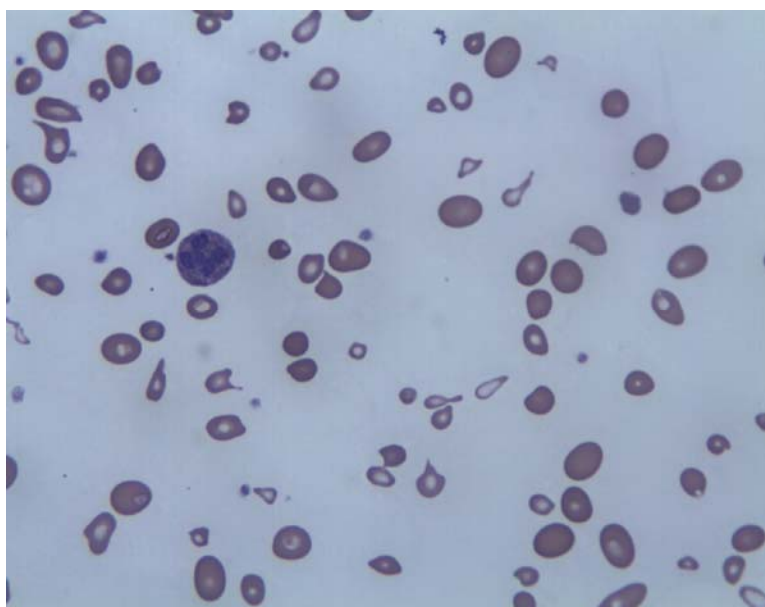
### **Case Presentation:**

Our patient was a 39-year-old African American woman admitted directly from clinic for hemoglobin of 4.8. She had a past medical history of hypertension, hypothyroidism status post thyroidectomy secondary to Graves' disease, and Myasthenia gravis status post thymectomy. Her symptoms began 5 months prior to presentation and consisted of fatigue and weakness, which became acutely worse 10 weeks prior to presentation when she was diagnosed and treated for a urinary tract infection. She noted worsening dyspnea on exertion and occasional episodes of chest pain with exertion. She denied heavy menstrual bleeding, hematemesis,

hematochezia or melena. Review of systems showed unintentional weight loss of 10 pounds over 3 weeks. She denied decreased appetite, felt that she had occasionally poor dietary choices and reported craving ice (pagophagia) for several months. Her home medications included levothyroxine, which she had not taken for approximately two weeks. As for her family history, both her father and sisters had anemia. There was no known history of sickle cell disease, thalassemia, or G6PD deficiency.

On physical exam the patient's vital signs were within normal limits. She was a thin appearing young woman with pertinent findings of exophthalmos, ptosis with a positive "curtain sign," pale mucous membranes and a soft systolic murmur on cardiac auscultation. Laboratory markers showed a macrocytic anemia with hemoglobin of 4.8, hematocrit of 13.5, mean corpuscular volume of 102, red cell distribution width of 48, reticulocyte count 8.6 and iron studies and hemoglobin electrophoresis within normal limits. Additional labs showed a normal folic acid level of 35.6 (3-16 ng/mL), a vitamin B12 of 178 (254-1230 pg/mL), haptoglobin < 6 (16-200 mg/dL), LDH > 1200 (90-190 U/L), TSH of 34.3, and a free T4 of 1.9. The peripheral blood smear showed macrocytic hypochromic anemia with many ovalocytes, marked anisopoikilocytosis, moderate polychromasia, and hypersegmented polymorphonuclear leukocytes (Fig 1). Additional work-up for vitamin B12 deficiency revealed homocysteine greater than 57 (0-13  $\mu$ mol/L), methylmalonic acid of 18420 (87-318 nmol/L), negative anti-gastric parietal cell antibodies and positive intrinsic factor-blocking antibodies.

Given the findings on peripheral blood smear and confirmatory testing, a diagnosis of Pernicious Anemia was made. The patient was started on Vitamin B12 replacement and scheduled for outpatient follow-up.



*Figure 1: Peripheral Blood Smear showing macrocytic ovalocytes with hypersegmented neutrophil and teardrop cells*

## **Discussion:**

Cobalamin or vitamin B12 deficiency is caused by insufficient dietary intake or impaired intestinal absorption. The incidence of B12 deficiency from insufficient dietary intake is less common given the increasing amount of cobalamin enriched foods. Causes of malabsorption are varied and can be attributed to Inflammatory Bowel

Disease, Celiac disease, post-surgical resection, achlorhydria, bacterial overgrowth, parasitic infections, or intrinsic factor deficiencies. Pernicious anemia is the second most common cause of B12 deficiency. It is an autoimmune disease characterized by destruction of parietal cells which secrete intrinsic factor which binds B12 during digestion and facilitates absorption in the ileum. It is often associated with other autoimmune diseases such as Grave's disease<sup>4</sup> and the clinical presentation involves the gradual onset of glossitis, cheilosis and neurologic abnormalities. The human body ordinarily has sufficient B12 stores in the bone marrow to last 2-3 years. However when B12 is depleted, normal erythropoiesis is halted which leads to immature red blood cells that are trapped in the bone marrow, with subsequent intramedullary lysis. This intramedullary lysis is responsible for an elevated LDH and decreased haptoglobin, which would ordinarily be seen in a hemolytic anemia. However, in the case of B12 deficiency there is an absence of schistocytes on the peripheral blood smear and the Direct Coombs test is negative. The peripheral blood smear classically shows ovalocytes with hypersegmented neutrophils. Additional laboratory findings include the presence of anti-intrinsic factor antibodies and anti-parietal cell antibodies, which have replaced the use of the Schilling Test<sup>3</sup>. The presence of anti-parietal cell antibodies has a sensitivity and specificity of 81.5% and 90.3%, respectively while anti-IF antibody test has a sensitivity and specificity of 37% and 100%, respectively. The combination of both antibody tests has a sensitivity and specificity of 73% and 100%, respectively<sup>5</sup>.

Further lab markers such as homocysteine and methylmalonic acid (MMA), are useful in the evaluation of megaloblastic anemias secondary to vitamin B12 or folic acid deficiency. The conversion of homocysteine to methionine in the cytoplasm requires both folic acid and vitamin B12 as cofactors, whereas the conversion of MMA to succinyl-CoA in the mitochondria requires only vitamin B12 as a cofactor. Therefore only homocysteine would be elevated in folate deficiency but both homocysteine and MMA are elevated in B12 deficiency.

Treatment of Pernicious anemia and other causes of B12 deficiency are usually treated with intramuscular injections of B12, but large doses of vitamin B12 has been shown to have the same efficacy. Large oral doses of B12 are thought to be absorbed “en masse” by an unknown mechanism. Randomized studies have found that patients treated with oral vitamin B12 is just as effective as those that are treated with intramuscular injections<sup>7</sup>.

### **Conclusion:**

Anemia is a common presentation in both inpatient and outpatient settings. In determining the etiology, the presence of other autoimmune disorders along with the findings of macrocytic ovalocytes with hypersegmented neutrophils on peripheral blood smear, should raise the suspicion for pernicious anemia.

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## **Protothecosis: a unique diagnosis of cellulitis**

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### **Introduction:**

*Prototheca* is a ubiquitous, achlorophyllic alga that was originally described by Krüger in 1894 as slime on broad-leaved trees that was non-pigmented, unicellular, immobile and heterotrophic that reproduced exclusively through forming endospores<sup>5</sup>. *Prototheca* has been found worldwide to cause disease in deer, cats, dogs, bats, and rarely humans; however, the number of human cases has steadily increased in the last two decades. The two species that cause disease in humans are *Prototheca wickerhamii* and *Prototheca zopfii*, with the former predominating.

### **Case Presentation:**

Here we describe a 58 year old Caucasian man with past medical history of COPD on home oxygen and chronic oral corticosteroid therapy presenting with a 5 month history of right hand pain, swelling and pruritis leading to numerous excoriations. He describes symptoms beginning after a peripheral intravenous line was placed for an outpatient screening colonoscopy, but have progressively worsened with diffuse erythema, serosanguinous drainage and worsening pain. He denies fevers, chills, weakness, numbness, or any risk factors for HIV infection. The patient has seen multiple physicians, and was prescribed clindamycin and sulfamethoxazole/trimethoprim with no improvement noted during outpatient therapy. On physical examination, the patient was afebrile and the dorsum of the right hand was erythematous with diffuse excoriations (see Figure 1 & 2). The erythema tracked proximally 5cm past the wrist without crepitus. No focal abscess or fluid collections were found. Sensation, grip strength, peripheral pulses and range of motion were intact. On further questioning, the patient states he routinely goes “noodling,” a method of barehanded fishing in freshwater in which he allows a fish to bite his own hand, and noted that 6 months before this admission he sustained abrasions from a catfish bite to his right hand. Upon admission, the patient was treated with cefepime and vancomycin with no clinical improvement noted. He then underwent biopsy of the right hand lesion that showed *Prototheca* infection. He was started on amphotericin B for 2 weeks and was discharged on voriconazole by mouth for 6 weeks.



Figure 1. Dorsum of right hand with erythema, edema and excoriations



Figure 2. Lateral border and proximal extension of erythema

## Discussion:

Since the original case report of human protothecosis was described in 1964<sup>4</sup>, there have been about 120-130 cases reported worldwide; most described cases have come from North America and Asia<sup>12</sup>. The majority of patients with protothecosis are immunocompromised, on chronic immunosuppressive therapy, HIV/AIDS, malnutrition or history of malignancies such as Non-Hodgkin's Lymphoma and chronic leukemia<sup>2,3,8</sup>. *Prototheca* has been isolated from slime flux on trees, drinking water, wastewater, soil, animal excrement<sup>12</sup>. Due to the dearth of patients, epidemiology of protothecosis is difficult to establish.

There are three main forms of protothecosis that have been described: cutaneous/subcutaneous, olecranon bursitis, and systemic involvement<sup>8,12</sup>. Cutaneous/subcutaneous infections account for a majority of cases in humans. Trauma to the skin and inoculation with colonized water has been found to be the most common route of infection in humans<sup>13</sup>. There is usually an incubation period of several weeks between inoculation and infection<sup>10</sup>. The original case, much like the case presented here, demonstrated a patch of dry, atrophic, depigmented skin with a well demarcated edge described as pruritic<sup>4</sup>. Also, presenting skin lesions have been described as erythematous nodules, plaques, superficial ulcers, and pustules<sup>7,10</sup>. Olecranon bursitis and fascia inflammation, which account for approximately 20 cases, does not generally occur in immunocompromised individuals, but like cutaneous protothecosis, occurs after injury to the skin over the joint or hematogenous spread<sup>12</sup>. Systemic, or disseminated, protothecosis has been documented in patients with HIV/AIDS, myasthenia gravis, diabetes mellitus, and end-stage renal disease on intermittent hemodialysis<sup>12</sup>.

The differential diagnosis for a persistent hand infection presenting like protothecosis includes sporotrichosis, *Mycobacterium marinum* and cutaneous nocardiosis<sup>10</sup>. Skin scrapings, grown in Sabouraud's agar at 30-32°C, are used to evaluate the skin condition. Examined microscopically under wet mount with lactophenol blue, hyperkeratosis and fungus-like organisms are seen with suppurative and granulomatous infiltration<sup>4,8,10</sup>. *Prototheca* usually appears as a uninucleate, ovoid organism between 3- $\mu$ m in length but can be seen as binucleate or quadrinucleate depending on the stage of mitotic activity. Also, microscopic examination shows characteristic endosporulating sporangia<sup>8</sup>. *Prototheca* species are glucose and lactose fermenting, and the

organisms stain well with the Periodic acid-Schiff stain, Giemsa stain and Gridley fungus stain<sup>4,8</sup>. In cutaneous infections, *Prototheca* is found infiltrating to the epidermal-dermal junction, causing increased lymphocyte and eosinophil aggregation<sup>4</sup>. A rapid real-time PCR / DNA resolution melting method has been described by Ricchi et al. that can aid in the quick and accurate diagnosis of protothecosis, identifying the organism and differentiating it from its spore-forming yeast counterparts<sup>9</sup>. Treatment with amphotericin B has been shown to be most effective in treatment of *Prototheca* infections<sup>12</sup>. Other treatments that have been efficacious include voriconazole, itraconazole and ketoconazole<sup>10,12</sup>.

### **Conclusions:**

The ubiquitous *Prototheca* species, although still a rare pathogen, is increasingly important in immunocompromised patients, and thus should remain on the differential diagnosis for persistent cutaneous infections, particularly of the upper extremities and face. New diagnostic modalities, such as real-time PCR, provide quick and definitive diagnosis of protothecosis in animals and humans, allowing for more timely treatment. Amphotericin B is the agent of choice for initial medical treatment, and surgical excision can prove to be definitive in cutaneous and bursal cases.

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