CLINICAL CARE CONUNDRUM

The approach to clinical conundrums by an expert clinician is revealed through presentation of an actual patient's case in an approach typical of morning report. Similar to patient care, sequential pieces of information are provided to the clinician who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

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One Hundred Years Later

A 36 year-old male physician was admitted to a Baltimore hospital in April 1907 with weight loss, weakness, arthralgias, and abdominal distension that had progressed over 5 years.

In 1907, major causes of unexplained weight loss included tuberculosis, hyperthyroidism, cancer, and diabetes. Arthralgias and weakness are not specific. The insidious progression over 5 years narrows the infectious possibilities; tuberculosis and syphilis are important considerations. Since surgical removal was the main treatment for malignancy in 1907, a history of prior surgery might point to a previously diagnosed malignancy that is now progressing.

Five years earlier, while visiting Turkey as a medical missionary, he first noted the onset of arthralgias that lasted 6 to 8 hours and occurred 3 to 4 times per week. Over time, these attacks lasted up to 24 hours and became associated with warmth, swelling, and tenderness of both small and large joints. He gradually lost weight and strength. One year prior to arrival in the hospital, he developed a cough productive of yellow sputum. Seven months prior, he returned from Turkey to Atlanta and noticed an increase in his cough, along with fevers of 100° Fahrenheit and night sweats.

The primacy of the arthralgias in this illness lead me to consider primary rheumatic diseases, and multisystem diseases (including infections) with a predominant skeletal component. In 1907, tests for lupus and the rheumatoid factor were not available. Neither skeletal remains nor works of art provide evidence that rheumatoid arthritis existed until the 19th century, whereas ankylosing spondylitis, gout, and rickets were present by then.

As a medical missionary, he might have acquired a disease endemic to the areas he visited, or the travel history may be a red herring. Familial Mediterranean fever, though prevalent in Turkey and a cause of arthralgias accompanied by recurrent attacks of abdominal pain and fever, is not an acquired disease.

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Behcet's disease, also known as Silk Trader's Route disease, is found in descendents of the countries that comprised the ancient Silk Route from Japan to the Middle East and may cause arthritis along with oral ulcers, genital lesions, pathergy or uveitis. I would inquire about his ancestry and fevers before dismissing these possibilities.

Although 5 years would be unusually long for tuberculosis to go unrecognized, a physician in the first half of the 20th century would place tuberculosis near the top of possible diagnoses. In 1930, a time when the population of the United States was considerably less, there were over 300,000 cases of tuberculosis. Physicians, and in particular pathologists since autopsies were more commonly performed, often died from tuberculosis since streptomycin, the first antituberculous medication, did not arrive until 1944. At the turn of the 20th century, the ability to detect tubercle bacilli was quite good. Thus, I would include tuberculous peritonitis as a cause of the progressive abdominal symptoms in this physician. In approximately one-third of patients with tuberculous peritonitis there is evidence of pulmonary disease, and I would try to culture tuberculosis in samples of sputum, a test then so common it probably rivaled our frequent complete blood counts in popularity.

Six months prior, examinations of sputum were negative for tubercle bacilli. Four months prior to arrival, the patient moved to New Mexico. His cough improved but he continued to lose weight and had diarrhea consisting of 3 to 4 loose or semiformed bowel movements per day. Three months prior to admission, he noted an increase in abdominal girth along with right lower quadrant fullness. One month prior, he noted painful swelling and warmth in both ankles as well as dyspnea with exertion.

The increased abdominal girth in the context of chronic illness might be due to ascites, adenopathy, visceromegaly, or mass lesions such as a neoplasm or abscess. If ascites is the cause, one would need to consider primary hepatic disorders, as well as extrahepatic diseases that could progress over years. Infection with hepatitis A virus does not cause chronic liver disease. Hepatitis B, in those days, was referred to as "serum hepatitis," and a serum marker for the B virus—the Australia antigen—was not identified until 1967. Cardiac causes of ascites include congestive heart failure and constrictive pericarditis, the latter an important consideration because it is potentially curable. Also, constrictive pericarditis can present as an indolent weight-losing disease because of chronic visceral congestion. Other considerations include nephrotic syndrome, infection, and neoplasm, including mesothelioma.

Abdominal distention might also be seen with a smoldering abscess. In addition to an appendiceal process, the travel and right lower quadrant localization reminds us to consider ameboma. This patient surely was in an area where amebiasis was endemic, and ameboma—a chronic inflammatory form of infection with *E. histolytica* not associated with diarrhea or liver cysts—may mimic cecal carcinoma. Exertional dyspnea suggests at least the possibility of cardiac disease. Despite the negative sputum cultures, tuberculosis remains high on the list as a cause of constrictive pericarditis or peritonitis, either of which may occur in the absence of active pulmonary disease.

Past medical history included measles and whooping cough as a child, mild pleurisy at age 14, mild influenza 7 years previously. The patient had a tonsillectomy as a child and had a portion of his inferior turbinate bone removed in an attempt to relieve a nasal condition.

On physical exam, the patient was thin and the skin over his face and hands was deep brown. His temperature was 101.5° Fahrenheit, the heart rate was 100, and the respiratory rate was 24. Small lymph nodes were palpable in the axillary and epitrochlear areas. His thorax moved asymmetrically, with less movement on the left apex and slight dullness to percussion in that area. The pulmonic component of the second heart sound was mildly accentuated. The abdomen displayed fullness and tympany, most pronounced in the right lower quadrant without hepatosplenomegaly. The left ankle was swollen, and the overlying skin was tense, shiny, and hot. On both lower legs, areas of discoloration and slight induration were observed, felt to be consistent with faded erythema nodosum.

Though pleurisy has numerous causes, its presence raises the specter of tuberculosis again. The nasal condition triggers thoughts of Wegener's granulomatosis or lethal midline granuloma, both unlikely diagnoses here. The pulmonary exam suggests an apical process, such as tuberculosis,

and the accentuated pulmonic heart sound implies pulmonary hypertension, which could be due to a number of chronic pulmonary diseases. The epitrochlear nodes are of interest since lymphoma and Hodgkin's disease rarely involve this area; syphilis and human immunodeficiency virus (HIV) are a few of the chronic diseases that may involve this lymph node region. More helpful is the absence of hepatosplenomegaly, since many indolent malignancies and infections would be expected to enlarge these organs by this point.

Monoarticular arthritis is often due to infection, and less likely due to rheumatoid disease. When rheumatoid arthritis flares, the entire skeleton flares, not single joints. Given the indolence and this single joint involvement, tuberculosis again comes to mind.

I would next want to obtain a plain chest radiograph, looking for evidence of tuberculosis. As with any test, one should ask how this will change management. In 1907, antituberculous medications were not available, so therapy was directed at lowering oxygen tension in the primary site of infection; for example, pulmonary disease was addressed via pneumothorax. If the chest radiograph provides little hint of tuberculosis, then consideration must be given to exploratory surgery of the abdomen given the focal abnormality in the right lower quadrant.

A peripheral blood smear revealed a hypochromic microcytic anemia. The total red blood cell count was 4.468 million/mm^3 (normal range for men is 4.52-5.90 million/mm^3), white blood cell count was 8180/mm^3, including 80% granulocytes and 9% eosinophils. On gross inspection, the stool was clay-colored, and stool microscopy demonstrated large numbers of neutral fat droplets, but no ova, parasites, or tubercle bacilli. Urinalysis revealed no albumin or casts, and the bones were normal on ankle radiographs. Another sample of sputum revealed no tubercle bacilli, and intradermal placement of tuberculin provoked no reaction.

His negative tuberculin skin reaction is unusual for that era, because of the prevalence of tuberculosis. Most likely, he is anergic because of his severe underlying illness, and the absent reaction is thus not all that helpful a clue. Multiple negative sputum examinations lower the possibility of pulmonary, but not extrapulmonary, tuberculosis. The absence of bony destruction on ankle radiographs lowers my suspicion for tuberculous arthritis.

The excess stool fat implies steatogenic diarrhea from malabsorption, and 2 categories here are pancreatic and luminal diseases. Of these 2, pancreatic etiologies produce more severe malabsorption. We do not hear mention of jaundice, however, and I cannot see how to link the pancreas to the arthritis. A chronic infection which may produce malabsorption and eosinophilia is strongyloidiasis, endemic in the southeastern United States. However, this patient did not manifest the most common finding of chronic strongyloidiasis, namely asthma. Adrenal insufficiency, as might result from disseminated tuberculosis, is associated with increased skin pigmentation, diarrhea, and eosinophilia. However, the diarrhea of adrenal insufficiency is not malabsorptive, and serum electrolytes and cortisol tests were not available then to confirm this diagnosis antemortem.

In an attempt to identify a unifying cause of chronic arthritis, malabsorption, and increased skin pigmentation, I must consider Whipple's disease first and foremost. Physicians then were strapped and observation was often the default mode of the day. Given the abdominal findings, an exploratory laparotomy would be warranted if his condition deteriorated.

Despite forced oral feedings, the patient continued to lose weight, from his normal of 175 pounds to a nadir of 145 pounds. Because of worsening abdominal distention, the patient underwent exploratory abdominal surgery on the twenty-first hospital day. Intraoperatively, no ascites was seen, but his mesenteric lymph nodes were hard and markedly enlarged. The abdomen was closed without further intervention. Two days after the surgery, the patient abruptly developed dyspnea. His respirations were 40 per minute, heart rate was 120, and he had minimal rales at the lung bases without findings of consolidation. He died 2 hours later, on the twenty-third hospital day, and an autopsy was performed.

The final event may have been a pulmonary embolism. As for the adenopathy, lymphoma and tuberculosis are possible. Heavy chain disease, an unusual lymphoproliferative disorder found in persons from the old Silk Trader's Route from the

Middle East to the Orient, is a remote prospect. However, 5 years is just too indolent for most cancers and would be very unusual for tuberculosis. I think the findings support Whipple's disease, and I wonder if this was the first reported case.

On postmortem examination, the abdominal adenopathy was striking. The small intestine contained enlarged villi with thickened submucosa, and the mesenteric nodes were enlarged with fat deposits and abnormal "foamy cells." Within these foamy cells, microscopy revealed numerous rod-shaped organisms. All studies were negative for tuberculosis, and although the pathologist, Dr. George Hoyt Whipple, suspected an infectious etiology, he offered the name "intestinal lipodystrophy" to emphasize the striking small intestinal changes he witnessed at autopsy, and which are the hallmarks of the disease that now bears his name. Whipple also shared the 1934 Nobel Prize in Physiology or Medicine with Minot and Murphy for their discovery that a nutritional substance in liver, now known as vitamin B12, was beneficial in treating pernicious anemia.

COMMENTARY

This is the index case of Whipple's disease, summarized from the original 1907 description.[1] George Hoyt Whipple, then a pathologist at Johns Hopkins, highlights the value of keen observation and a well-done case report in describing a new disease entity. One of the roles of case reports is to detail the features of an unknown disease. In this capacity, Whipple's summary is exemplary. His achievement was having the openness of mind to realize he was witnessing something novel, and to take the first step on the road to discovery. Although Whipple suspected he was staring at a unique disease, he could not pinpoint the culprit bacteria and he had trouble squaring the extraintestinal findings with the marked intestinal anomalies. It was left to decades of input from others to confirm the association of arthralgias, eosinophilia, skin hyperpigmentation, and cardiac valve abnormalities with intestinal malabsorption, and to culture the infectious agent.

In his discussion, Whipple recognized he was confronted with a novel clinical entity. Prior to surgery, pulmonary and mesenteric tuberculosis were suspected, based on the fevers, weight loss, cough, fat malabsorption, and lymphadenopathy. However, he felt the left apical exam was more representative of retraction from prior disease than active infection. He was also bothered by the negative skin reaction and sputum tests. At surgery, the pronounced adenopathy suggested sarcoma or Hodgkin's disease but postmortem examination eliminated these possibilities. At autopsy, the abdominal findings were most striking. The small intestine demonstrated enlarged villi with thickened submucosa and markedly enlarged mesenteric lymph glands containing large fat deposits and "distinctly abnormal foamy cells." These foamy macrophages contained "great numbers of rod-shaped organisms resembling the tubercle bacillus." However, all tests were negative for tuberculosis, and the lungs contained no active disease. Though he suspected an infectious etiology, Whipple offered the name "intestinal lipodystrophy" to emphasize the striking small intestinal pathology.

Although Whipple had surmised a novel infectious agent in 1907, it took almost a century to isolate the causative microbe. Granules within foamy macrophages of the small intestine were detected on periodic acid-Schiff (PAS) staining in 1949.[2] Similar PAS-positive granules were soon discovered in other tissues and fluid, providing a plausible explanation for the systemic features of the disease.[3] Electron microscopy confirmed the presence of infectious bacilli in 1961,[4] ushering in the era of antimicrobial treatment for this disease. More recently, using polymerase chain reaction (PCR), a unique bacterial 16S ribosomal RNA gene was isolated in patients with Whipple's disease.[5,6] Phylogenetically classified with the actinobacteria, *Tropheryma whipplei* (fom the Greek *trophe*, nourishment, and *eryma*, barrier) was ultimately subcultured in 2000,[7] and immunodetection testing became possible. Using this technique, the archived pathology specimens from the 1907 index case demonstrated numerous intracellular bacteria in the lamina propria, closing the loop started by Whipple nearly a century earlier.[8]

Whipple's index case report described most of the manifestations of the disease we are familiar with today. As in the original description, arthralgias are the most common initial symptom and may precede diagnosis by a mean of 8 years. Other cardinal features include weight loss, abdominal pain and steatorrhea due to small intestinal involvement. Table 1 summarizes the

TABLE 1
Clinical Features of Whipple Disease

Clinical Feature	Comment
Cardinal features (present in 60% to 90%)	
Arthropathy	Most common initial symptom, preceding diagnosis by a mean of 8 years. Migratory, nonerosive, mainly in the peripheral joints.
Weight loss	
Diarrhea	Usually steatorrhea, may be associated with pain or occult blood in the stool
Other common features (present in 20% to 45%)	
Fever	
Lymphadenopathy	May present as a palpable mass
Increased skin pigmentation	Mechanism unknown (evidence of adrenal insufficiency has not been found in Whipple's)
Cardiac disease	Culture-negative endocarditis
Hypotension	
Peripheral edema	
Uncommon clinical features	
Central nervous system involvement	May be global (dementia, personality change, sleep disturbance) or focal (cranial neuropathy, nystagmus)
Eye disease	Uveitis, retinitis
Hepatosplenomegaly	
Polyserositis	
Ascites	

Two pathognomonic involuntary muscle signs in CNS Whipple disease are oculomasticatory and oculo-facial-skeletal myorhythmia.[10]

important signs and symptoms of Whipple's disease.[9,10] One notable manifestation missing in Whipple's report is central nervous system involvement. Central nervous system (CNS) disease ranges from cognitive deficits to encephalitis and focal defects, and may occur years after treatment and without concomitant intestinal symptoms.

A remaining mystery is why this pathogen results only rarely in clinical disease. Caucasians comprise the majority of infected patients, and men are affected 8 times more often than women. An overrepresentation of HLA-B27 suggests a genetic predisposition, though its role in pathogenesis is unclear. *T. whipplei* has been identified by PCR methods in asymptomatic individuals, implying additional abnormalities must be present in susceptible hosts for symptoms to occur following colonization.[11] The exact immune defects are speculative, and immunodeficiency states (such as HIV) have not been consistently identified in patients with Whipple's disease.

The cornerstone of diagnosing Whipple's disease is upper endoscopy with duodenal biopsy. Flattening of the villi and markedly increased PAS-positive staining of lamina propria macrophages are strongly suggestive of the diagnosis. PAS-positive staining is not unique to *T. whipplei*, however. In patients with profound immunodeficiency, *Mycobacterium avium intracellulare* may stain positive with PAS. Since Whipple's disease is only rarely associated with HIV, a negative HIV test would favor a diagnosis of Whipple's disease. Electron microscopy may distinguish *T. whipplei* from its mimickers by morphology. For extraintestinal disease, PCR testing on samples from infected tissue has been found to be a reliable diagnostic aid.[9]

Given the rarity of the disease, controlled clinical trials addressing optimal treatment are lacking. Current recommendations include initial therapy for 14 days with an agent that crosses the blood-brain barrier (eg, ceftriaxone) to reduce the incidence of CNS disease. This is then followed by a year or more of oral antimicrobial therapy with trimethoprim-sulfamethoxazole or a tetracycline.[9] While most patients respond within 2 to 3 weeks, relapse may occur in as many as one-third of patients.

Historical case reports reinforce the case-based learning paradigm. As the discussant remarks, observation was all too often the only recourse for physicians a century ago. In recounting the 7-year progression of disease in 1 individual, Whipple provides a unique window into the natural evolution of the key features of this systemic disease. Viewed through the prism of Whipple's eyes, we can recall the striking lymphoid hyperplasia and unusual organisms in the small intestine, cementing our understanding of the pathogenesis of this disorder. Revisiting past cases allows us to learn of and learn from the past.

Teaching Points

1. Whipple's disease should be considered in patients with unexplained arthralgias accompanied by weight loss, malabsorption, and abdominal pain.
2. For suspected intestinal Whipple's disease, diagnosis is best made by duodenal biopsy demonstrating PAS-positive staining in lamina propria macrophages.
3. Systemic manifestations of Whipple's disease include culture-negative endocarditis and CNS

disease. PCR testing of involved sites for *T. whipplei* is recommended to confirm extraintestinal disease.

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REFERENCES

1. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. *Bull Johns Hopkins Hosp*. 1907;18:382–391.
2. Black-Schaffer B. The tinctoral demonstration of a glycoprotein in Whipple's disease. *Proc Soc Exp Biol Med*. 1949; 72:225–227.
3. Fleming JL, Wiesner RH, Shorter RG. Whipple's disease: clinical, biochemical, and histopathologic features and assessment of treatment in 29 patients. *Mayo Clin Proc*. 1988;63:539–551.
4. Yardley JH, Hendrix TR. Combined electron and light microscopy in Whipple's disease: demonstration of "bacillary bodies" in the intestine. *Bull Johns Hopkins Hosp*. 1961;109:80–98.
5. Wilson KH, Blitchington R, Frothingham R, Wilson JAP. Phylogeny of the Whipple's disease-associated bacterium. *Lancet*. 1991;338:474–475.
6. Relman DA, Schmidt TM, MacDermott RP, Falkow S. Identification of the uncultured bacillus of Whipple's disease. *N Engl J Med*. 1992;327:293–301.
7. Raoult D, Birg ML, La Scola B, et al. Cultivation of the bacillus of Whipple's disease. *N Engl J Med*. 2000;342: 620–625.
8. Dumler SJ, Baisden BL, Yardley JH, Raoult D. Immunodetection of *Tropheryma whipplei* in intestinal tissue from Dr. Whipple's 1907 patient. *N Engl J Med*. 2003;348: 1411–1412.
9. Marth T, Raoult D. Whipple's disease. *Lancet*. 2003;361: 239–246.
10. Louis ED, Lynch T, Kaufmann P, et al. Diagnostic guidelines in central nervous system Whipple's disease. *Ann Neurol*. 1996;40:561–568.
11. Ehrbar HU, Bauerfeind P, Dutly F, et al. PCR-positive tests for *Tropheryma whippleii* in patients without Whipple's disease. *Lancet*. 1999;353:2214.