CLINICAL PRACTICE

*Exercises in Clinical Reasoning***Sutton's Law: Keep Going Where The Money Is**

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CASE DESCRIPTION

A 70-year-old Japanese man presented to a local clinic with a 3-year history of weight loss and a 2-month history of anorexia. His baseline weight was 60 kg, which had decreased to approximately 50 kg at the time of presentation. He denied fever, chills, night sweats, arthralgia, rash, diarrhea, and vomiting. His past medical history included hypertension. He was not taking any medications. The patient was a retired real estate manager. He did not drink alcohol and had quit smoking tobacco 40 years prior. He never used illegal drugs and was not sexually active.

This is a 70-year-old Japanese man with 3 years of unintentional weight loss. Unintentional weight loss of nearly 15 % warrants investigation. In the present case, the duration of 3 years indicates a relatively slow process. In addition to depression, the differential diagnosis is broad, but in an elderly patient, depression and access to food should be evaluated. Because weight loss is a non-specific symptom, specific diagnostic clues should be sought through physical and laboratory examinations. It is important to determine whether the patient has had age-appropriate cancer screening.

Developing an accurate problem representation is an indispensable step in the process of clinical reasoning. The problem representation at the beginning of a case, especially one in which the chief complaint is non-specific like “weight loss,” results in a broad differential diagnosis. The clinician acknowledges this and naturally requests additional data in an attempt to narrow the differential diagnosis.

A physical exam at the local clinic revealed cachexia and normal vital signs. The heart, lung, abdominal, and lymph

node exams were normal. The laboratory results are shown in Table 1. The patient had mild anemia and hypoproteinemia. As intra-abdominal diseases were suspected because of his anorexia, computed tomography (CT) and magnetic resonance imaging (MRI) scans of the abdomen revealed multiple retroperitoneal mass lesions and intra-abdominal lymph nodes 1 to 2 cm in size.

The patient now presents with a 15 % weight loss of 3 years' duration, anemia, hypoalbuminemia, renal dysfunction, intra-abdominal lymphadenopathy and multiple small retroperitoneal mass lesions. The differential diagnosis at this point includes infectious diseases (e.g., tuberculosis, fungal and parasitic infections), malignant tumors (e.g., pancreatic cancer, lymphoma, and liposarcoma), and non-infectious inflammatory diseases (e.g., sarcoidosis, immunoglobulin G4-related disease [IgG4-RD], and Castleman disease). Given the gravity of the aforementioned diagnoses, a biopsy of the intra-abdominal lymphadenopathy should be pursued.

The physician acknowledges the seriousness of the considered diagnoses and requests a biopsy. This exemplifies Sutton's law in clinical reasoning, which is avoidance of tests that are unlikely to be diagnostic and the preferential pursuit of tests thought to be of highest diagnostic value—in this case, a biopsy. Clinicians tend to apply Sutton's law in high-stakes circumstances. For example, if a patient with cancer, who just returned from a long flight, presents with pleuritic chest pain, tachycardia, and shortness of breath, the clinician may immediately obtain a CT angiogram of the chest to evaluate for a pulmonary embolus as opposed to ordering a chest x-ray and d-dimer test.

The patient was subsequently referred to the department of surgery at our hospital and underwent a laparoscopic biopsy of an intra-abdominal lymph node located near the superior mesenteric artery. At this visit, the patient reported a new complaint of 2–3 loose bowel movements a day.

An elderly patient with chronic weight loss, diarrhea, and lymphadenopathy may be suffering from a gastrointestinal disorder due to one of the aforementioned infections or cancers. A non-infectious inflammatory condition such as inflammatory bowel disease or a malabsorption disorder such as

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Table 1 Laboratory Test Results at the Time of Admission to (1) the Department of Surgery, (2) the Department of Medicine, and (3) the Department of Emergency Medicine and Hospitalization

	Date 03/29/XX (1)	Date 09/03/XX (2)	Date 12/03/XX (3)	Normal range
Blood test				
Leukocyte	8500/ μ l	6000/ μ l	8300/ μ l	3900–9000/ μ l
Hemoglobin	10.5 g/dl	8.1 g/dl	9.2 g/dl	13.5–17.4 g/dl
Hematocrit	32.1 %	24.8 %	28.4 %	40.0–52.0 %
Mean corpuscular volume	88.7 %	89.2 %	88.2 %	84.0–97.0 %
Platelet	22.0×10^4 / μ l	19.2×10^4 / μ l	16.8×10^4 / μ l	13.0 – 40.0×10^4 / μ l
Blood urea nitrogen	21.5 mg/dl	17.7 mg/dl	20.8 mg/dl	8.0–22.0 mg/dl
Creatinine	1.23 mg/dl	0.98 mg/dl	0.96 mg/dl	0.61–1.04 mg/dl
Sodium	134 mEq/l	133 mEq/l	129 mEq/l	136–147 mEq/l
Chloride	103 mEq/l	102 mEq/l	101 mEq/l	98–109 mEq/l
Potassium	4.3 mEq/l	4.6 mEq/l	4.8 mEq/l	3.6–5.0 mEq/l
Glucose	99 mg/dl	110 mg/dl	18 mg/dl	90–109 mg/dl
Total protein	4.9 g/dl	4.4 g/dl	4.8 g/dl	6.7–8.3 g/dl
Albumin	2.4 g/dl	2.2 g/dl	2.3 g/dl	3.8–5.0 g/dl
Total bilirubin	0.7 mg/dl	0.5 mg/dl	0.9 mg/dl	0.3–1.2 mg/dl
Aspartate aminotransferase	27 U/l	34 U/l	201 U/l	10–40 U/l
Alanine aminotransferase	13 U/l	15 U/l	55 U/l	5–40 U/l
Alkaline phosphatase	362 U/l	325 U/l	2186 U/l	115–359 U/l
Calcium (corrected)	7.8 (9.6)mg/dl	8.1 (9.7)mg/dl	7.4 (9.7)mg/dl	8.5–10.2 mg/dl
Lactate dehydrogenase	150 U/l	207 U/l	248 U/l	115–245 U/l
Erythrocyte sedimentation rate	N/S	20 mm/hr	15 mm/hr	2–17 mm/hr
C-reactive protein	3.69 mg/dl	1.23 mg/dl	2.66 mg/dl	<0.30 mg/dl
Urinalysis				
Occult hematuria	–	–	–	–
Urinary protein	1+	–	–	–
Pyuria	–	–	–	–

celiac disease is also possible. Stool samples should be evaluated for indolent infections, as mentioned above, and a serologic test for celiac disease should be performed. However, the highest diagnostic yield likely remains within the pathology of the abnormal lymph nodes.

The clinician has a well-developed diagnostic scheme for diarrhea, which includes malabsorptive, infectious, malignant, and non-infectious inflammatory causes. Inductive reasoning may be a useful form of clinical reasoning in cases in which pattern recognition is challenging.¹ When the patient develops diarrhea, the clinician faces the dilemma of deciding whether or not the symptom constitutes a late-appearing diagnostic clue. The clinician has difficulty prioritizing the list of possible diagnoses, as the majority can result in weight loss, diarrhea, and lymphadenopathy. Again demonstrating Sutton's law, he feels that the highest diagnostic yield is within the pathology of the lymph nodes.

A repeat intra-abdominal lymph node biopsy was performed (Fig. 1). Microscopy of the biopsy tissue revealed non-caseating granuloma with infiltration of foamed macrophages, lymphocytes, plasma cells, foreign-body giant cells, and surrounding adipose tissue. The cell surface marker and chromosome banding test results were normal, and the immunohistochemical staining for IgG4-RD was negative.

Despite the presence of non-caseating granulomas, the pathologic findings are not consistent with the features of

tuberculosis or sarcoidosis, since there was no presence of acid-fast bacilli or epithelioid histiocytes, respectively. Causes of granulomatous diseases involving foreign-body giant cells include exposure to foreign bodies such as silicon or oil, but the patient has no known history of such exposure. Careful re-examination of the biopsy specimens should be pursued, as they are not currently diagnostic, although interpretation was not different between the two biopsy specimens.

The clinician is puzzled by the pathology results of foreign-body granuloma. Using Sutton's law, he requests re-examination of the pathologic specimen, as he believes that it's where the diagnosis (money) is. He realizes that clinico-pathological correlation is essential in this complex case.

Fig. 1 Finding of repeated laparoscopic intra-abdominal biopsy (lesion is indicated by blue circle)

After the patient was discharged from the department of surgery, he continued having anorexia and loose stools. Two months later, he was re-referred to our emergency department from the clinic physician and was hospitalized due to an episode of hypoglycemia (serum glucose of 18 mg/dl) and somnolence. He regained normal mental status after receiving a glucose infusion. Physical examination revealed tachycardia and generalized pitting edema in all extremities as well as conjunctival pallor and mild abdominal distension. A regimen of antifungal therapy (amphotericin B) was administered for suspected fungal infection based on a positive finding in the periodic acid–Schiff (PAS) and Grocott's methenamine silver (GMS) stain discovered on re-examination of the intra-abdominal lymph node biopsy. However, empiric antifungal therapy did not lead to clinical improvement of the anorexia and loose stools.

The patient's altered mental status was likely from hypoglycemia, as he fulfills Whipple's triad, which is (1) hypoglycemia, (2) symptoms of hypoglycemia, and (3) resolution of symptom with correction of plasma glucose level. The differential diagnosis for hypoglycemia is broad, but in a patient with weight loss, diarrhea, and lymphadenopathy, possible causes include a malabsorption disorder such as celiac disease, adrenal insufficiency from an infiltrative fungal process like histoplasmosis, or depletion of glycogen stores in the liver due to long-term anorexia from underlying malignancy.

The pallor likely reflects worsening of the patient's anemia. The generalized pitting edema may suggest worsening of hypoalbuminemia, possibly from diarrhea. Other causes of hypoalbuminemia—heart failure, renal failure, nephrotic-range proteinuria, and cirrhosis—warrant consideration. The abdominal distention may reflect the development of ascites.

The initial hematoxylin and eosin staining of lymph node tissue was unrevealing; however, the GMS and PAS presented “positive staining suggestive of possible fungal infections.” Although definitive antifungal therapy should be initiated once the microbiological diagnosis is confirmed, empirical

Fig. 3 Microscopic finding of the intra-abdominal lymph node biopsy specimen (lesions are indicated by blue circles)

antifungal therapy may be needed if a patient's clinical status is unstable or deteriorating. Amphotericin B is one of the best choices due to its activity against a broad spectrum of fungal pathogens, including yeast, endemic mycosis, and mold.

The clinician acknowledges the broad differential for hypoglycemia but restates the problem representation, “... in a patient with weight loss, diarrhea, and lymphadenopathy...” to narrow the diagnostic possibilities.

In addition to the results of repeated laboratory studies (Table 1), the serum concentrations of vitamin B12, folate, and iron were normal. The abdominal CT scan showed a moderate volume of ascites with multiple retroperitoneal mass lesions (Fig. 2). The blood culture was sterile for bacteria, mycobacteria, and fungi. The ascites was aspirated and subsequently analyzed to reveal a cell count of 91/μl, albumin level of 0.3 g/dl, adenosine deaminase level of 5.5 U/l (normal range, 5.0–20.0 U/l), negative malignant cells, and negative bacterial culture. Because of possible military tuberculosis or hematological disease, a bone marrow examination was conducted, but revealed no abnormalities.

The ascites and bone marrow examinations provide no significant clue for diagnosis. The serum-to-ascites albumin

Fig. 2 Abdominal CT scan showing retroperitoneal mass lesions (indicated by blue circles)

Fig. 4 Periodic acid–Schiff (PAS) stain of the specimen

Fig. 5 Grocott's methenamine silver (GMS) stain of the specimen

Fig. 7 Electron microscopy image of the intestinal villi revealing numerous bacterial rods

gradient is 2.0 (2.3–0.3), indicating portal hypertension or increased portal hydrostatic permeability. An upper endoscopy with biopsy of the small intestine may be indicated for evaluation of a possible malabsorptive syndrome such as celiac disease.

Microscopic re-examination of the intra-abdominal biopsy specimen again showed non-caseating granulomas with infiltration of foamy macrophages, lymphocytes, plasma cells, foreign-body giant cells, and surrounding adipose tissue (Fig. 3). Although Gram and Ziehl–Neelsen stains were negative, the PAS (Fig. 4) and GMS stains (Fig. 5) were positive. The cell surface marker and chromosome banding test were normal, and the immunohistochemical staining for IgG4-RD was negative.

An esophagogastroduodenoscopy showed disseminated yellowish-white villi from the duodenum to the upper small intestine (Fig. 6). A biopsy demonstrated tissue that stained positive for PAS.

Disseminated yellowish-white villi with positive PAS staining strongly raises a concern for Whipple's disease. Electron microscopy, as well as immunohistochemical

staining and genetic tests, should be performed to confirm this rare diagnosis.

The revised problem representation is now as follows: a 70-year-old cachectic Japanese man with retroperitoneal lymphadenopathy, yellowish-white villi with positive PAS staining, weight loss, and chronic diarrhea. The physician immediately recognizes the correct diagnosis. This is an example of pattern recognition (non-analytic reasoning). This case illustrates that, sometimes, reasoning by Sutton's Law—going where the money is (high-yield tests and biopsies)—is necessary in such a complicated case.

Electron microscopy of the intestinal villi revealed numerous bacterial rods (Fig. 7). Immunohistochemistry for *Tropheryma whipplei* was positive (Fig. 8), as was the polymerase chain reaction (PCR) test for *Tropheryma whipplei*. A diagnosis of Whipple's disease was made.

Ceftriaxone was initiated, but the patient experienced rash, fevers, and chills. As we could not differentiate between an adverse drug reaction and immune reconstitution inflammatory syndrome, antibiotics were changed to

Fig. 6 Esophagogastroduodenoscopy showing disseminated yellowish-white villi (blue circle) in the upper small intestine

Fig. 8 Immunohistochemistry finding positive for *Tropheryma whipplei*

meropenem, to be followed by oral sulfamethoxazole/trimethoprim. The patient's symptoms gradually improved.

DISCUSSION

In 1976, the bank robber Willie Sutton is thought to have said that he robbed banks because that was where the money was. Clinicians may use such a tactic—pursue the test of highest diagnostic yield while avoiding lower-yield tests—in reasoning when the stakes are high and/or a particular test is thought to be inevitable.²

For example, a patient with 90 % stenosis of the left anterior descending artery, as detected on an angiogram 1 year prior, presents with a self-limited episode of chest pain. His troponin levels are undetectable, and electrocardiograms show prior Q waves in the anterior leads. The physician may elect to pursue an angiogram and not waste time or resources with a functional study; a normal nuclear stress test would not adequately reduce the post-test possibility of unstable angina or progressive coronary artery disease.

In this case, the discussant's reasoning followed the maxim, "tissue is the issue." He demonstrated Sutton's law by requesting a biopsy early in the case and continued to focus on tissue as the key to diagnosis. He did not waste time or resources with repeat imaging or serum tests.

This case demonstrates an atypical presentation of an uncommon disease. A suspected diagnosis of Whipple's disease early in the patient's presentation would have been difficult, as the classic presentation of Whipple's disease is years of large-joint migratory arthralgia followed by severe gastrointestinal symptoms—diarrhea, weight loss, and abdominal pain. However, utilizing Sutton's law, the discussant was able to arrive at the correct diagnosis.

CLINICAL TEACHING POINTS

1. Whipple's disease is a rare infectious disease characterized by diarrhea, weight loss, abdominal pain, and arthralgia.³
2. Diagnosis requires a high index of suspicion, and is often based on pathological findings and PCR results,⁴⁻⁶ which may not readily be available.
3. Whipple's disease is often misdiagnosed. If correctly diagnosed, however, it responds well to antimicrobial therapy, and the treatment is likely to lead to a cure.
4. There are times when additional procedures (immunohistochemistry, electron microscopy, and PCR testing) beyond simple staining of the biopsy specimen are necessary to disambiguate histopathological findings unexplained by conventional staining.

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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