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From Microcytosis to Macrodiagnosis

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A 12-year-old Hispanic girl presented with fatigue, lightheadedness, and intermittent headaches. She was depressed and appeared pale to her mother. Her examination was unremarkable except for palpebral conjunctival pallor and was otherwise noncontributory. She had a profound hypoproliferative microcytic anemia with low iron level, low transferrin saturation, and a normal ferritin level. The patient experienced improvement in clinical symptoms following transfusion of packed red blood cells and oral iron therapy. At follow-up 2 months later, she presented with similar symptoms and persistent microcytic anemia with low iron levels. Her ferritin level was increased along with markedly elevated C-reactive protein and erythrocyte sedimentation rate. An oral iron challenge demonstrated lack of absorption, and hepcidin level was also significantly elevated. Thorough gastrointestinal and rheumatologic evaluations were performed to search for a source of inflammation. Key components of the patient's social history supplemented by serology, radiographic, and pathologic findings ultimately cinched an unexpected diagnosis.

DR ZOE HARNENZ (PEDIATRIC RESIDENT)

A 12-year-old Hispanic girl presented with fatigue, lightheadedness, pale skin, mild intermittent headaches, and depressed mood. The patient was obese, leading to school bullying and intentional 2-kg weight loss over the months before presentation; she also had not gained weight in the previous 3 years, resulting in a drop in BMI from 25 to 23.2 between the ages of 8 and 12. She denied fever, pain, nausea, night sweats, or respiratory symptoms. What are your initial thoughts?

DR NURA EL-HAJ (PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOW)

The patient presented with nonspecific symptoms such as pallor and lightheadedness that may suggest anemia. In an adolescent girl, symptomatic anemia raises the suspicion of iron deficiency anemia (IDA) due to menorrhagia. In addition to blood loss, other etiologies of iron deficiency include insufficient dietary intake of iron, as well as lead intoxication, which is uncommon in this age group. Additional history and examination should be obtained to guide further investigations.

DR HARNENZ

The patient reported irregular "very light" menstrual cycles since menarche at age 11, with last menses 2 months before presentation. She denied apparent bleeding, had a balanced diet but poor appetite, and had no history suggesting lead exposure or pica. She denied abdominal complaints. She had some right ankle pain resulting from a previous talus fracture with osteonecrosis. She appeared comfortable. She weighed 61 kg (94.6th percentile), her height was 162 cm, and her BMI was 23.2. Her temperature was 36.3°C, blood

abstract

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Dr Karakas provided the images from the diagnostic imaging (radiology) department, conceptualized and contributed to this case report, drafted the initial manuscript, and reviewed and revised it multiple times; Dr Cham provided the gross and microscopic images from the pathology department, conceptualized and contributed to this case report, drafted the initial manuscript, and reviewed and revised it multiple times; Drs El-Haj, HarnEnz, Singer, Kim, Ling, Nguyen, and Petru conceptualized and contributed to this case report, drafted the initial manuscript, and reviewed and revised it multiple times; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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pressure was 114/61 mm Hg, heart rate was 115 beats per minure, and respiratory rate was 18 breaths per minute with oxygen saturation of 100% in room air. Her skin and palpebral conjunctivae were pale. Cardiovascular and respiratory systems were normal, other than notable tachycardia. Her abdominal examination was soft but full, without masses, tenderness, or hepatosplenomegaly. Her right ankle had a well-healed scar. No rash was present. A chest radiograph was obtained to evaluate for cardiomegaly (in the setting of severe anemia). Her chest radiograph revealed no cardiopulmonary abnormalities. What other diagnostic investigations would you consider now?

DR SYLVIA SINGER (PEDIATRIC HEMATOLOGY/ONCOLOGY)

We would obtain a complete blood cell count to confirm the clinical suspicion of anemia and determine if this is, in fact, a microcytic process, because a low mean corpuscular volume (MCV) would be expected in iron deficiency. If microcytic anemia is confirmed, iron level, transferrin level, transferrin saturation, total iron-binding capacity (TIBC), ferritin, and free erythrocyte protoporphyrin (FEP) can be obtained to assess elemental iron transport and storage. Other causes of microcytosis include hemoglobinopathies and lead exposure, both of which are unlikely in this patient, given her age and clinical presentation. Other cell lines and a peripheral smear should also be examined to screen for a malignant process.

DR HARNENZ

Hemoglobin was 5.7 g/dL (reference range 11.8–15 g/dL), with MCV of 57 fL (reference range 73–93 fL). Reticulocyte count was 1.6% (reference range 0.5%–1.5%), red cell distribution width 29.9% (reference range 11.5%–14.5%). Platelet count was 659 000 per mm^3 (reference range 150 000–400 000 per mm^3). The remainder of her complete blood cell count and differential was within normal limits, without lymphopenia or eosinophilia. Blood smear revealed platelets of normal size, hypochromia without abnormal cells. Serum iron level was low (11 μg/dL; reference range 37–145 ug/dL), with a transferrin saturation of 3% (reference range 20%–50%). TIBC (315 μg/dL) and transferrin levels (256 mg/dL) were within normal range (reference ranges 240–450 μg/dL and 200–360 mg/dL, respectively). Ferritin level was 51.8 ng/mL (reference range 10–150 ng/mL). FEP was significantly elevated (>600 ng/dL; reference range 0–80 ng/dL). Hemoglobin electrophoresis and lead level were normal. The patient received 1 U of packed red blood cells, increasing her hemoglobin to 6.9 g/dL, and started oral iron therapy (2 mg/kg per dose twice daily) with improvement in clinical symptoms. However, the patient presented 2 months later with similar findings of fatigue and microcytic anemia (hemoglobin 7.7 g/dL, MCV 62 fL). Serum iron level remained low (9 μg/dL). Ferritin was 100.2 ng/mL and reticulocyte count was 1.1%. In conjunction with her history, would these laboratory findings alter our initial differential diagnosis?

DR EL-HAJ

This clinical presentation does not support overt blood loss as an etiology for IDA. Whereas ferritin increased, the hemoglobin remained persistently low with low iron levels despite oral iron supplementation. The differential diagnoses ought to be broadened to include inappropriate iron absorption, chronic occult blood loss, and chronic inflammation. Low ferritin, an acute phase reactant, is sensitive and specific for iron deficiency. However, normal to elevated levels in the setting of low iron studies suggest inflammation or infection. Importantly, thrombocytosis, seen in reactive inflammatory states, can also be noted in the context of IDA, making the platelet count a less useful marker of inflammation. Additional inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) would be helpful to obtain. Occasionally, iron deficiency due to low intake or increase loss overlaps with anemia of inflammation, which disrupts iron absorption and mobilization. An oral iron challenge and hepcidin level should be considered to evaluate iron absorption. Moreover, the patient's weight loss, albeit reported as somewhat intentional, should trigger a more thorough gastrointestinal investigation.

DR VIVIEN NGUYEN (PEDIATRIC GASTROENTEROLOGY)

To assess for inflammation in the gastrointestinal tract, in addition to the inflammatory markers, fecal calprotectin level and stool testing for occult blood were performed. CRP and ESR were both elevated: 128.9 mg/L (reference range 0–5 mg/L) and >105 mm/hour (reference range 0–13 mm/h), respectively. Fecal calprotectin was borderline elevated (97 μg/g; reference range ≤49 μg/g), and the result of stool testing for occult blood was negative. Esophagogastroduodenoscopy and colonoscopy were performed to further investigate gastrointestinal sources of blood loss. Esophagogastroduodenoscopy was normal, but scattered aphthae were noted in the cecum on colonoscopy.

DR HARNENZ

An oral iron challenge (4 mg elemental iron per kg)

demonstrated complete lack of absorption: pre- and postdose levels were 17 and 22 μg/dL, respectively. However, she responded to initial intravenous iron administration with an increase in reticulocyte count from 1.1% to 1.8% in 4 days. Hepcidin level was significantly elevated at 216.1 ng/mL (reference range 4.4–47.3 ng/mL). Repeat FEP remained elevated at 448 ng/dL. What do these findings suggest?

DR SINGER

Markedly elevated FEP, ESR, CRP, and hepcidin suggest inflammation as the basis for low iron levels and severe anemia with disruption in iron metabolism and absorption. The duodenal iron absorption blockade is bypassed by intravenous iron. The elevated FEP does not distinguish iron deficiency from anemia of chronic disease (ACD), because both demonstrate iron-restricted erythropoiesis. At this point, it is essential to pursue additional investigations to uncover an underlying source of inflammation.

DR NGUYEN

From a gastroenterology perspective, the mild, nonspecific endoscopic findings do not support inflammatory bowel disease as a cause for the patient's condition. However, mucosal disease beyond the endoscope's reach is not excluded. Cross-sectional imaging to assess for small bowel Crohn's disease should be considered.

DR HARNENZ

In the interim, given the elevated inflammatory markers and mild endoscopic findings, rheumatology was also consulted. Dr Ling, what rheumatologic etiologies were entertained and what investigations were undertaken?

DR NICOLE LING (PEDIATRIC RHEUMATOLOGY)

Although this patient did not have malar, discoid, photosensitive, or vasculitic rash, nasopharyngeal ulceration, or arthritis, the constellation of symptoms prompted a rheumatologic evaluation, including laboratory evaluation for systemic lupus erythematosus. Her rheumatologic workup was overall unremarkable: findings included negative antinuclear antibody, double-stranded DNA, Smith, ribonucleic protein antibody, antiphospholipid antibodies including anticardiolipin antibody, β-2 glycoprotein, lupus anticoagulant, and direct antiglobulin test. C4, urinalysis, creatinine, and urine protein/creatinine ratio were all normal. C3 was mildly elevated (177 mg/dL; reference range 82–163 mg/dL) and thought to be an acute phase reactant. An echocardiogram was negative for pericardial or pleural effusion.

When patients present with nonspecific symptoms such as fatigue and weight loss in the context of elevated inflammatory markers, further imaging to look for occult vasculitis is recommended. This patient had equal pulses in all extremities and a normal echocardiogram result (both of which could be abnormal in Takayasu arteritis, a large vessel vasculitis). Mild ulcerations on endoscopy can be seen in patients with Behçet's, another form of vasculitis, but this patient did not have recurrent oral or genital ulceration, pathergy, uveitis, or rash. Antineutrophil cytoplasmic antibodies were negative.

DR HARNENZ

In the absence of a clear diagnosis and while awaiting pending rheumatologic studies, a tuberculin skin test (TST) was placed in anticipation of a possible need for high-dose steroid therapy. In addition, for completeness in the setting of vague presenting features, computed tomography (CT) of the chest and abdomen were obtained as recommended by rheumatology and gastroenterology consultants to exclude occult processes. CT scan of the abdomen revealed a large complex pelvic mass (12.3 × 12.7 × 10 cm) (Fig 1). The mass was superior to the urinary bladder. The uterus and the ovaries were not seen as separate structures. There was evidence of marked inflammation and lymphadenopathy. Chest CT was normal. Dr Karakas, can you comment on these images?

DR PINAR KARAKAS (PEDIATRIC RADIOLOGY)

The patient's ovaries were not distinguished as separate structures on CT, so the leading differential diagnosis for this pelvic mass was a germ-cell or other ovarian tumor. Nonetheless, inflammatory reactions (fat stranding, appendix inflammation, paracolic and mesenteric adenopathy) were noted and not felt to be typical of adnexal masses. Given these findings, a desmoplastic small round cell tumor, a myofibroblastic tumor, or a primary mesenteric gastrointestinal stromal tumor were considered. MRI was recommended to provide further radiographic characterization.

DR HARNENZ

MRI of abdomen and pelvis revealed the large complex pelvic mass and adjacent inflammatory reaction, mesenteric and paracolic lymphadenopathy, that appeared similar to the CT findings. Ovaries were identified, displaced by the mass, but without primary involvement (Fig 2).

DR KARAKAS

The most important finding on the MRI was identifying the ovaries as separate structures near the mass.

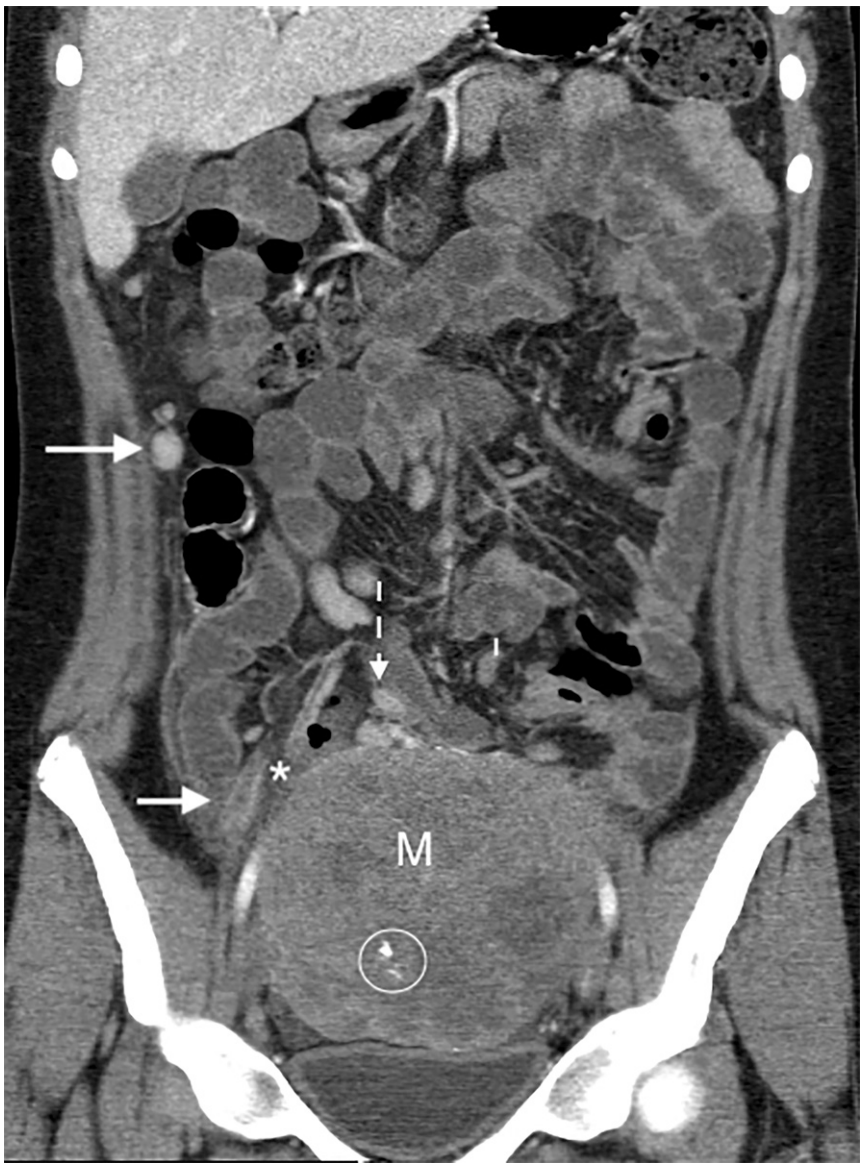

FIGURE 1
Coronal CT image of the abdomen and pelvis after intravenous contrast administration: Large complex pelvic mass (M) with cystic and solid components with scattered tiny calcifications (circle). Inflammatory reaction around the mass with omental and mesenteric fat stranding (asterisk); proximal appendix inflammation (short arrow) and multiple inferior mesenteric (dashed arrow) and ascending paracolic lymphadenopathy (long arrow).

This decreased the likelihood of an adnexal origin mass. On the basis of the MRI, a mesenteric tumor with inflammatory reaction was thought to be more likely.

DR HARNENZ

Tumor markers for an ovarian germ-cell tumor were nonetheless obtained for completeness: α-fetoprotein, quantitated β-human chorionic gonadotropin, and carcinoembryonic antigen levels were normal, whereas cancer antigen 125 was mildly elevated (44 U/mL; reference range <35 U/mL). Dr Kim, you were involved in the case, given the concern for possible neoplasm and the need for a tissue diagnosis. Can you describe your surgical findings?

DR SUNGHOON KIM (PEDIATRIC SURGERY)

The patient underwent exploratory laparotomy. The mass was found to be mobile, arising from the mesentery of the distal ileum. The appendix was adherent to the mass, without tumor extension into the appendix. The mass was resected along with associated mesentery and appendix by using a bipolar electrosurgical device (Fig 3). Further exploration revealed normal appearing ovaries, liver, peritoneum, small bowel, and colon. Enlarged lymph nodes within the adjoining mesentery were noted, and few were included in the surgical specimen. Malignant and benign lesions are considered in the differential diagnoses of abdominopelvic masses in children. In this population, solid and cystic lesions of the gastrointestinal tract, omentum, and mesentery are less frequently encountered. In female adolescents, germ cells and ovarian tumors are the most common. The presence of a robust inflammatory response leading to low iron mobilization was also suspicious for an inflammatory myofibroblastic tumor. Although uncommon in children, this entity, characterized by the proliferation of myofibroblasts admixed with predominantly mononuclear inflammatory cells, may present in the abdominopelvic cavity.

DR HARNENZ

In the interim, the previously placed TST had 11 mm of induration, interpreted as positive on the basis of the patient's history of travel to high-prevalence regions of the world, residence in California, and lack of history of bacille Calmette-Guérin (BCG) vaccination. Her

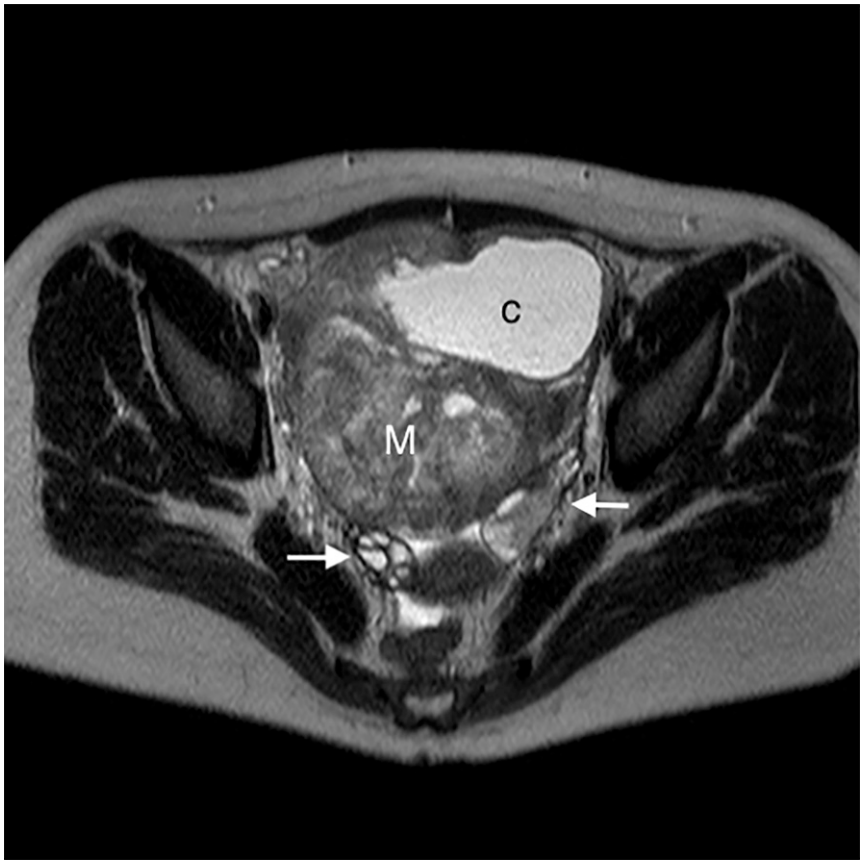

FIGURE 2
MRI of the pelvis with axial T2 single shot sequence: large 393 complex pelvic mass (M) showing heterogeneous enhancement and diffusion restriction with solid and cystic (C) components is located anterior to the ovaries (arrows), which appear separate from the mass.

QuantiFERON-TB (QFT) blood test for tuberculosis (TB) was also positive (TB1-NIL and TB2-NIL >10 IU/mL). The infectious diseases service was then consulted. Dr Petru, what did this consultation uncover?

DR ANN PETRU (PEDIATRIC INFECTIOUS DISEASES)

Further history revealed that the patient was born in the United States and lives in northern California. Her only clear TB risk factor was travel to high-TB prevalence regions of the world. She had traveled for several weeks at least twice in the previous 2 years to visit her extended family in Mexico; she also traveled to Puerto Rico for a wedding and to Texas and Los Angeles. The patient had not received the BCG vaccine. She had no known contact with anyone with symptoms of TB. Her aunt had a history of a positive TST but was never symptomatic. Our patient also had previous reactive TSTs on several occasions since early childhood, per mother's memory and her own report, but without known measurements; neither her aunt nor our patient were treated for latent TB. Her 11-mm TST induration was just above the cutoff for positivity (normal <10 mm). The QFT was obtained to confirm her infection and was definitely and significantly positive. In addition, further history revealed that our patient's varied diet included soft unpasteurized cheese, "queso fresco," eaten in Mexico and often brought to the United States by family members. Pathology review provided key information. Dr Cham, can you tell us what you saw?

DR ELAINE CHAM (PATHOLOGY)

There was no evidence of hemorrhage in the mass or vascular invasion to explain the patient's profound anemia. Pathology revealed extensive granulomas with inflammatory cells and cell necrosis without evidence of malignant cells. Careful analysis of the resected mass revealed acid-fast bacilli (AFB) throughout the mass, including in the wall and lumen of the appendix (Fig 4). A frozen sample from the mass was positive for *Mycobacterium tuberculosis* complex using a polymerase chain reaction test (not US Food and Drug Administration approved for this use). Other studies using fixed and frozen samples were negative by broad-range bacterial polymerase chain reaction. Frozen samples processed for *Mycobacterium tuberculosis* DNA by using hsp65 amplified probe were also negative. *Coccidioides* serology by immunodiffusion and *Histoplasma capsulatum* antibody by complement fixation and immunodiffusion were all negative, as was serum for HIV-1 p24 Ag and HIV-1,2 antibodies. After ~10 weeks of incubation, a single colony of *Mycobacterium bovis* grew from a frozen section of the mass, with pyrosequencing revealing no mutations to suggest resistance to isoniazid, ethambutol, or rifampin, but the isolate was resistant to pyrazinamide.

DR PETRU

After the mass resection and review of pathology, it became clear that the patient had extrapulmonary TB involving the abdomen and pelvis with an enlarged omental node that

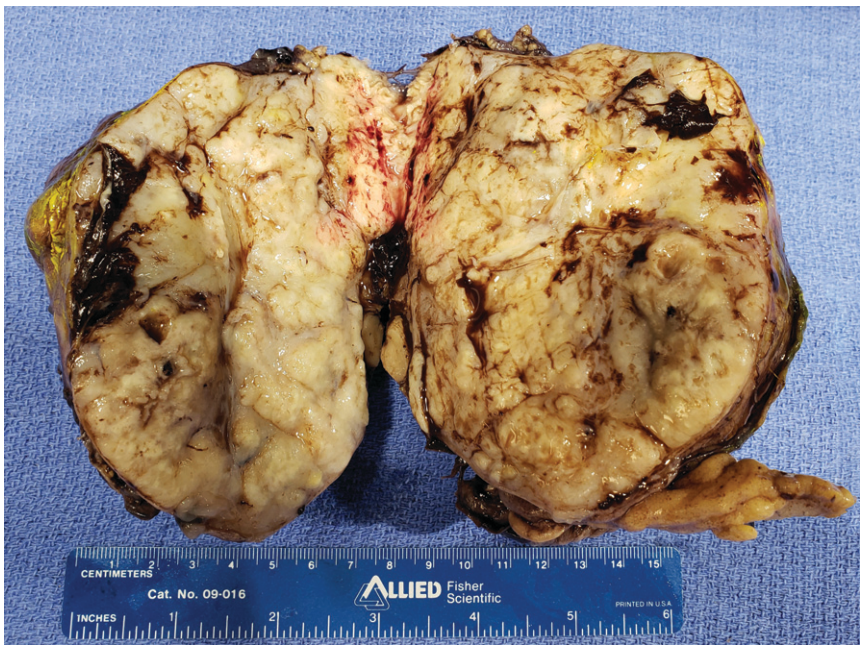

FIGURE 3
A large cystic and solid abdominal mass with necrotic features was removed.

likely grew over many years. During that time, the patient remained mostly asymptomatic. However, it caused sufficient inflammatory reaction to adhere to adjacent structures, likely resulting in anorexia, weight loss, and chronic anemia.

DR HARNENZ

How was this patient treated and can you comment on her clinical outcomes?

DR PETRU

The patient was initially treated with 10 weeks of isoniazid, rifampin, ethambutol, pyrazinamide, and vitamin B_6. When *M bovis* was identified, she was continued on isoniazid, rifampin, and vitamin B_6 and eventually completed 9 months of therapy. Results of laboratory studies 6 months after resection were normal or significantly improved: hemoglobin 14.3 g/dL, platelets 236 000 per mm^3, ESR 21 mm/hour, CRP 0.8 mg/L, iron 91 μg/dL, transferrin 303 mg/dL with 22% saturation, TIBC 411 μg/dL, ferritin 29 ng/mL, FEP 80 ng/dL, and hepcidin 9.7 ng/mL. Repeat abdominal and pelvic MRI result was normal, without signs of residual or recurrent disease. She has regained the weight she lost before her surgery and diagnosis and currently weighs 96.3 kg (BMI 35.9). In retrospect, she reports a markedly improved sense of well-being and absence of abdominal discomfort (that she thinks she did not recognize, likely because the mass was probably very slow growing).

SUMMARY AND COMMENTARY

In this case we highlight findings of a florid inflammatory state in a 12-year-old patient who presented with microcytic anemia, weight loss, and fatigue. Testing, in this case, initially focused on identifying suspected gastrointestinal or rheumatologic etiologies. At presentation, there were no clues of a possible pelvic mass. In fact, even after the mass was identified radiographically, the patient declined feeling abdominal or pelvic discomfort. The diagnosis of extrapulmonary TB was established only after the mass was resected, and AFB were noted in the pathology specimen.

Some key laboratory features in this case include a markedly elevated FEP level. Both ACD and IDA reveal iron-restricted erythropoiesis causing elevated FEP. Differentiating between these is crucial: enteral iron repletion may not be useful in the setting of inflammation, and the underlying inflammatory triggers ought to be addressed. Additionally, although anemia with associated thrombocytosis may occur in the setting of inflammation, it is also important to recognize that these 2 entities occur in IDA, thereby posing diagnostic challenges.[1] Normal ferritin levels without correction of anemia after oral iron supplementation and a failed oral iron absorption test in our patient prompted further investigation of an inflammatory process in particular, given the significantly elevated CRP level. Our patient had a high hepcidin level, which normalized several months later. Hepcidin regulates and is regulated by iron levels. Hepcidin serum levels can differentiate between IDA and ACD[2]: levels are highest in inflammation, because inflammatory cytokines promote its transcription, and lowest in IDA. Less hepcidin is produced if inflammation occurs in combination with iron deficiency, as opposed to an iron-replete state.[3] As hepcidin assays become more routinely available, testing for hepcidin will be of valuable clinical significance to assist in differentiating ACD from IDA. Furthermore, parenteral iron bypasses the duodenal absorption blockade to allow erythropoiesis, and our patient responded to such treatment.

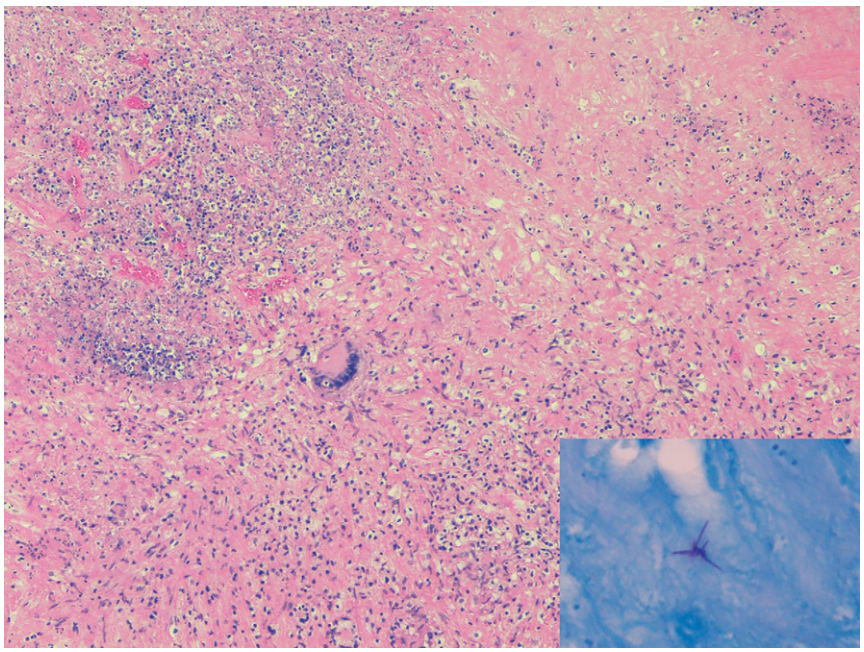

FIGURE 4
Necrotizing granuloma with a giant cell (×10, H&E stain). Positive for AFB (inset, 100×, Kinyoun stain).

The granulomatous findings and AFB found on histology, as well as positive TST and QFT further increased the likelihood of TB infection, narrowing the diagnosis to either *M tuberculosis* or *non-tuberculous Mycobacterium*. Of note, QFT is an interferon-γ release assay on blood that detects TB infection by quantifying the patient's interferon γ response to specific peptides associated with pathogens causing TB. The peptides used in this interferon-γ release assay simulate the proteins present in *M tuberculosis* complex organisms, including *M tuberculosis* and *M bovis,* but are absent in BCG vaccine strains.
Other granulomatous etiologies of mesenteric masses include *Coccidioides immitis*, endemic in areas through which the patient traveled in California's Central Valley, Texas, and Mexico.[4]
Tuberculoid granulomas caused by *H capsulatum* have rarely been described. Although also relatively unusual, extrapulmonary TB may mimic cancer, inflammatory, acute surgical, and gastrointestinal disorders such as appendicitis[4] and genitourinary tumors.[5,6] *M bovis*, which primarily affects cattle, is an important human pathogen causing extrapulmonary TB in children.[7] Extrapulmonary TB secondary to *M bovis* with a negative chest radiograph has been well described in Hispanic children in California and is the result of ingestion rather than inhalation.[8,9] *M bovis* has been isolated from unpasteurized soft cheese in Mexico[10,11] and in cheeses from Mexico entering the United States via noncommercial border crossings.
International travel and consumption of unpasteurized milk products are consistent among cases diagnosed with intraabdominal *M bovis* and frequently cause inflammation and granuloma formation and involve the appendix or lymph nodes.[12] In our patient's case, the granulomatous mass arose from the mesentery and was fixed to the appendix, with multiple enhancing abdominal lymph nodes on imaging. In a particularly poignant case of "abdominal cocoon syndrome" (sclerosing peritonitis), a 12-year-old Iraqi girl drank milk directly from a cow's udder. She had a dense fibrotic mass adherent to the abdominal wall, omentum, the right-sided adnexa, and appendix, with caseating granuloma on pathology, with *M bovis* isolated from peritoneal fluid.[13]
Treatment of *M bovis* is challenging, because it is universally resistant to pyrazinamide, requires a longer treatment course than *M tuberculosis*, and has higher mortality.[7,8] In our patient's case, fresh samples were not processed immediately for AFB stains and cultures. Fortunately, the organism was cultured from one of the frozen tumor samples, thereby confirming the diagnosis.
The unexpected source of IDA identified in this patient highlights the importance of considering unusual sources of an inflammatory state, including exposures to rare infectious organisms, even if the presenting symptoms are nonspecific. In retrospect, the documented positive TST and confirmatory Quantiferon TB test should have been recognized as strong clues of TB as the underlying cause of our patient's presentation. Had that happened, the surgical samples might have been processed when they were fresh rather than frozen, and we might have made the diagnosis more efficiently. We were fortunate that a single colony of *M bovis* was isolated from the frozen sample and enabled confirmation of the etiology. This case also highlights the interaction between inflammation and functional iron deficiency and the need to consider early parenteral treatment with iron when lack of enteral absorption is confirmed.

ABBREVIATIONS

ACD: anemia of chronic disease
AFB: acid-fast bacilli
BCG: bacille Calmette-Guérin
CRP: C-reactive protein
CT: computed tomography
ESR: erythrocyte sedimentation rate
FEP: free erythrocyte protoporphyrin
IDA: iron deficiency anemia
MCV: mean corpuscular volume
TB: tuberculosis
TIBC: total iron-binding capacity
TST: tuberculin skin test

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