Hepatic Sarcoidosis

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Abstract

Sarcoidosis is an idiopathic multisystem disease, characterized by non-caseating granulomas in affected organs. Pulmonary involvement is the most common site of disease activity, although the disease can also affect the liver, bone marrow, and heart. We report a case of symptomatic hepatic sarcoidosis in a 31-year-old African-Canadian woman which responded to treatment with doxycycline.

The patient was referred to internal medicine from a peripheral emergency department after presenting with fever, hepatitis, and thrombocytopenia with a computed tomography scan concerning for hepatic abscesses. The patient remained febrile with worsening liver enzymes despite broad spectrum antibiotics. An extensive infectious workup was negative. Biopsies of bone marrow and liver revealed non-caseating granuloma, and an elevated angiotensin-converting enzyme level. Doxycycline, initially started for presumptive infective etiology, led to rapid resolution of symptoms and normalization of biochemical markers. To our knowledge, this is the first case report of doxycycline used to treat hepatic sarcoidosis in Canada.

Résumé

La sarcoïdose est une maladie multisystémique idiopathique, caractérisée par la présence de granulomes non caséux dans les organes affectés. Les poumons sont le plus souvent le site de la maladie, quoique celle-ci se manifeste aussi dans le foie, la moelle osseuse et le cœur. Nous décrivons ici un cas de sarcoïdose hépatique symptomatique chez une afro-canadienne de 31 ans qui a répondu à un traitement à la doxycycline.

La patiente a été aiguillée en médecine interne par un service des urgences en périphérie après s'y être présentée avec de la fièvre, une hépatite et une thrombopénie et y avoir subi une tomodensitométrie relative à des abcès au foie. Malgré l'administration d'antibiotiques à large spectre, la patiente est demeurée fébrile et ses enzymes hépatiques ont continué de se dégrader. Les nombreux tests infectieux effectués se sont révélés négatifs. Des biopsies de la moelle osseuse et du foie ont révélé la présence de granulomes non caséux et un taux élevé de l'enzyme de conversion de l'angiotensine. La doxycycline, initialement administrée pour une étiologie infectieuse présumée, a rapidement entraîné la résorption des symptômes et la normalisation des marqueurs biochimiques. À notre connaissance, il s'agit du premier cas rapporté au Canada de traitement d'une sarcoïdose hépatique par la doxycycline.

A 31-year-old African-Canadian female presented to a peripheral community hospital complaining of fever and nonproductive cough for several days. Her only previous medical history was chronic thrombocytopenia without a diagnosis. She was not taking any prescription medications, natural health products, or over-the-counter medications. She was prescribed azithromycin and sent home for a presumed community-acquired pneumonia. She returned after two days, feeling increasingly unwell with myalgias, arthralgias, nausea and vomiting, right upper quadrant (RUQ) abdominal pain, and continued fever. Physical exam was significant for RUQ tenderness. Initial investigations revealed thrombocytopenia of $40 \times 10^9/L$ (range 150–400), lymphocytopenia of $0.3 \times 10^9/L$ (range 1.1–4.4), elevated C-reactive protein (CRP) of 293 mg/L (range 1.0 – 8.0), and a mixed hepatic injury pattern with total bilirubin 38 $\mu\text{mol/L}$ (range 2–20), ALP 323 U/L (range 40–135), GGT 587 U/L (range 12–43), ALT 291 U/L (range 4–55), and AST 454 U/L (range 5–35). Her INR was elevated at 1.8 (range 0.9–1.2). A chest radiograph showed no acute findings, and a normal cardiomeastinal silhouette. Computed tomography (CT) scan of her abdomen revealed hepatomegaly and multiple low attenuating hepatic and splenic lesions (Figure 1).

The patient was then referred to internal medicine for investigation of sepsis/hepatitis. She arrived on vancomycin, meropenem, and azithromycin and continued broad spectrum coverage for several days.

Figure 1 Contrast-enhanced computed tomography scan of the abdomen demonstrating hypoattenuating lesions in the liver and spleen.

She was found to have evidence of disseminated intravascular coagulation with hypofibrinogenemia of 1.54 g/L (range 2.16–4.36), an elevated D-dimer $>10,000 \text{ ug/L}$ (range <500), and coagulopathy and thrombocytopenia. Ferritin levels were markedly elevated on admission at 15 445 ug/L (range 10–200), with hypertriglyceridemia of 4.13 mmol/L (range 0.35–1.70). Peripheral smear showed no evidence of schistocytes. She developed a normocytic anemia of 90 g/L (range 120–160) with a negative hemolytic workup and no evidence of macroscopic bleeding. Electrolytes and renal function remained within normal limits throughout her admission. Serum *human chorionic gonadotropin* (HCG) was normal. Thyroid-stimulating hormone (TSH) and T4 were within normal range.

Autoimmune workup was unremarkable, with a negative anti-CCP, antinuclear antibodies (ANA), *anti-neutrophil cytoplasmic antibody* (ANCA), rheumatoid factor (RF), anti-liver-kidney microsomal (anti-KLM), anti-smooth muscle antibody, and antimitochondrial antibody (AMA). Serum immunoglobulins were normal. The patient had an elevated angiotensin-converting enzyme (ACE) level at 75 U/L (range 9–63). Ionized serum calcium and 24-hour urine calcium were normal.

Hematology recommended a bone marrow biopsy, which showed multiple non-caseating granulomas with no evidence of hemophagocytosis or malignancy, and stained negative for acid fast bacilli and fungal organisms. A bone marrow culture was obtained, and was negative for bacteria, fungi, and mycobacterium.

In conjunction with the infectious diseases consultant, an extensive infectious workup was performed, including: multiple negative blood cultures for bacteria, fungus and mycobacterium; negative malaria smears, negative urine culture, negative legionella urine antigen, negative urine chlamydia and gonorrhea, negative nasopharyngeal swab for viruses, negative heterophile antibody, negative human immunodeficiency virus (HIV) screen, negative hepatitis A virus (HAV) IgM, hepatitis B immune (negative HBV surface Ab, negative HBV core Ab, HBV surface antibody 68.2 IU/L), hepatitis C virus (HCV) Ab negative, hepatitis E virus (HEV) IgG+ IgM-, cytomegalo virus (CMV) IgG+ IgM-, Epstein-Barr virus (EBV) IgG+. Serology was negative for brucella, rickettsia, tularemia, coxiella, and entamoeba. On day 10, she was started on empiric doxycycline for presumed infectious etiology, as the results of the above investigations were not yet available.

On day 11, hepatology recommended a liver biopsy which was significant for granulomatous hepatitis, with multiple small non-caseating granulomas lacking fibrin rings or areas of central necrosis, staining negative for acid fast bacilli and fungal organisms, with no evidence of malignancy. As she had defervesced on doxycycline, her cholestatic liver enzymes began to normalize and there were case reports documenting response

of systemic sarcoidosis to doxycycline, the decision was made to continue doxycycline as therapy for sarcoidosis. Doxycycline was continued empirically for six weeks at 100 mg PO twice daily.

Just prior to discharge, the patient was incidentally found to have developed a dilated cardiomyopathy with an ejection fraction of 35% and areas of wall motion abnormalities noted on transthoracic echocardiogram. She was initiated on treatment with an ACE inhibitor and a beta-blocker, but was unfortunately lost to follow-up of presumed cardiac sarcoidosis after discharge.

Discussion

Sarcoidosis is an idiopathic systemic inflammatory disorder, with an estimated prevalence of 2–60 cases per 100,000 people.¹ Sarcoidosis has a higher prevalence rate in females, with an age peak of 20–40 years, and patients of African descent are affected at three times the population rate.¹ The pulmonary system is most commonly affected in over 90% of cases, though extra-pulmonary involvement can be seen in 40–50% of cases.¹ Other commonly affected sites include peripheral lymph nodes, liver, spleen, stomach, small bowel, bone, and skin. Chronic thrombocytopenia has been previously reported in the literature as a rare complication of sarcoidosis.² Less commonly reported manifestations include myopathy, uveitis,

granulomatous meningitis, facial nerve palsy, cardiomyopathy, and parotid enlargement.¹

Liver involvement has been identified in about 50–80% of patients with systemic sarcoidosis, although the majority of patients are asymptomatic.³ Clinically significant disease and abdominal pain occurs in less than 20% of sarcoidosis cases.¹ Only 10–30% of patients have elevated liver enzymes, and 40% of patients have hepatomegaly or splenomegaly.¹ Hepatomegaly is commonly identified on CT imaging with multiple hypodense hepatic lesions.⁴ Systemic features such as fever, fatigue, and arthralgias are present in the majority of patients with active liver sarcoidosis.¹ Longstanding disease may result in portal hypertension in 3–18% of patients and progression to cirrhosis, often with a worse prognosis than *primary biliary cirrhosis* (PBC).

Alkaline phosphatase can be elevated 5–10 times the upper limit of normal, while aminotransferase levels are usually mildly elevated compared to elevations in ALP (Figure 2). Serum ACE level is a widely-used diagnostic test for sarcoidosis. While global sensitivity for elevation of ACE level is only 60%,⁵ specificity is much higher at 90%.⁶ Although lacking sensitivity, an elevated ACE level is fairly specific for the diagnosis, particularly given the clinical context.¹ Serum ACE levels can be used as supportive evidence for the diagnosis of sarcoidosis but should not be used in

Figure 2. Biochemical response of ALP and platelet count after initiation of doxycycline.

isolation, as elevations can occur with disseminated tuberculosis, fungal infections, and hyperthyroidism.⁷ Liver biopsy in suspected sarcoidosis should be obtained if the diagnosis is uncertain and liver enzymes are elevated to at least twice the upper limit of normal. Granulomas are typically small, non-caseating and epithelioid, with negative staining for acid-fast bacilli and fungi.¹

Hepatic granulomas are present in approximately 4% of all liver biopsies, with causes including systemic infections, malignancy, drugs, immunologic disease, or idiopathic.⁸

In the developing world, infectious disease is the most common cause of hepatic granulomas.¹ Most infectious granulomas have some areas of necrosis. Infectious causes include: Q fever (*Coxiella burnetii*), cytomegalovirus, EBV, HCV, HBV, *mycobacterium tuberculosis*, and several fungal and parasitic infections. Several infectious causes are characterized by certain histological findings, such as fibrin rings in Q fever, *leishmania* and *rickettsia* infections; central necrosis in *mycobacterium tuberculosis*; and abscesses with *listeria* and *bartonella* infections.¹

The workup of any hepatic granuloma should include staining for acid-fast bacilli (AFB) and for fungi.⁸ Foreign bodies, such as talc in intravenous drug users, or suture material left over after surgery, can cause hepatic granulomas.⁸ This is usually made obvious from the clinical history. Hodgkin's lymphoma is identified as the cause of hepatic granulomas in 8–17% of cases. Other neoplastic etiologies include leukemias, gastrointestinal adenomas, and hepatocellular carcinomas.⁸

Non-infectious immunologic insults remain the most common cause of hepatic granulomas in the developed world.⁸ Causes include PBC and sarcoidosis, and rarely Crohn's disease and systemic vasculitis.⁸ Hepatic sarcoidosis should be distinguished from PBC. PBC typically has a positive AMA, while serum ACE levels are typically elevated in sarcoidosis. PSC does not show granulomas in the liver.¹

Treatment of hepatic sarcoidosis may be observation alone if asymptomatic or mild elevations of liver enzymes, and normal liver synthetic function. First line medical treatment

Appendix 1. Lab values.

Day	Hb	WBC	Plt	Ferr	D Bili	T Bili	ALT	AST	ALP	GGT	INR
1	138	3	77								
3	137	2.9	40		29	38	291	454	323	587	1.8
4	105	3.1	37		32	40	230	446	234	430	2.2
5	101	3.4	33	15445	50	71	203		245		1.5
6	107	4.2	33	14815	62	83	183	456	263	422	1.4
7	111	6.5	47	15644	68	92	167	446	338	500	1.3
8	106	8.5	59	14599	65	84	127	332	379	533	
9	101	7.3	67		53	70	100		586	736	
10	97	7.4	75		37	53	84		676	839	
11	90	6.2	67	8604	25	37	75		747	871	1.4
12	85	5.8	94		19	31	64		712	855	1.4
13	93	6.3	119		15	30	59		731	896	1.5
14	92	5.7	153		13						1.7
15	94	4.6	176		13	27	47		611	793	1.7
17	91	2.3	176			25	45	89	518	710	1.2
19	97	2	174	1955							
39	114	3.8	106			9	55	55	201	421	1.1
41	119	2.9	151	602		12	54	45	189	402	1.1
48	124	2.8	155			11	31	28	136		
82	132	3.4	154			6	22	21	104	124	
92	121	3.5	138			12	19	19	88	87	
103	128	3.2	149								1.2

includes corticosteroids and ursodeoxycholic acid, with some authors suggesting 12 months of therapy before dose tapering.¹ Ursodeoxycholic acid is relatively safer than long-term steroids, and some authors recommend starting with this before prednisone. Although these medications can help normalize laboratory values, serum liver enzymes can also normalize spontaneously, and it is unclear if steroids prevent long-term liver damage or halt progression of disease (see Appendix 1).¹

Several studies have shown that tetracyclines and their analogs are effective for mild sarcoidosis, while reducing corticosteroid requirements.^{9,10} In one study of patients with cutaneous sarcoidosis, ten out of 12 patients experienced a partial or complete response of their skin lesions to minocycline.¹¹ Proposed mechanisms include inhibition of matrix metalloproteases, angiogenesis, apoptosis, and granuloma formation in vitro.⁵ Doxycycline has been previously reported for the treatment of cutaneous and pulmonary sarcoidosis.¹²

This case highlights the clinical features of systemic sarcoidosis without pulmonary involvement, which occurs in only 10% of cases. Although hepatic involvement occurs in a majority of cases, symptomatic involvement is estimated to occur in only 20% of cases. Additionally, the value of considering the differential diagnosis of hepatic granulomas is discussed, and we revisit the diagnostic role of measuring ACE levels for suspected sarcoidosis.

Finally, although there are reported cases of cutaneous and pulmonary sarcoidosis responding to tetracyclines, we believe this is the first reported case of hepatic sarcoidosis exhibiting a response to treatment with tetracycline.

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