CASE REPORT

Granulomatous hepatitis in a patient with Crohn's disease and cholestasis

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Accepted 24 August 2017

SUMMARY

We describe a case of a 23-year-old woman with a history of Crohn's disease (CD), who initially presented with sepsis-like symptoms, subsequently developed severe cholestasis and following extensive inpatient workup was found to have non-caseating granulomas on her liver biopsy. Infectious aetiologies were excluded and the patient was treated with oral corticosteroids, which ameliorated but did not completely reverse the cholestasis. We review the differential diagnosis of hepatic granulomas and discuss the potential difficulties in establishing their exact aetiology in patients with CD.

BACKGROUND

Cholestasis coupled with systemic symptoms can pose a diagnostic conundrum in the setting of coexisting Crohn's disease (CD). We briefly review the literature on hepatic granulomas, a relatively rare manifestation of both extraintestinal CD and extrapulmonary sarcoidosis. We discuss the etiopathogenetic similarities between CD and sarcoid hepatic granulomas and propose that further research is needed to better characterise the relationship between the two overlapping disorders.

CASE PRESENTATION

A 23-year-old African-American woman with CD presented to the emergency department with nausea without vomiting, non-specific abdominal pain, chills and hypotension. There was no associated cough, dysuria or rashes.

Prior medical history was significant for Crohn's ileocolitis and perianal disease diagnosed in 2013, fistulotomy and diverting loop ileostomy in 2014 and recurrent hospitalisations for Crohn's flare-ups. The patient had been treated with azathioprine and prophylactic antibiotics (ciprofloxacin and metronidazole) with marginal success and was noted to be poorly compliant with her medications and follow-ups. She had been off her medications for several weeks prior to this presentation. Previous therapies included adalimumab (2013–2014), infliximab (discontinued after patient developed an infusion reaction to third induction dose in 2016) and corticosteroids, all of which resulted in inadequate disease control, in part due to poor medication compliance.

On examination, the patient's temperature was 38.6°C, heart rate 139 bpm and blood pressures in the 70/40 mm Hg. Abdomen was diffusely tender to palpation without guarding or rigidity. Perianal ulceration with some purulence was noted. Laboratory findings were significant for white blood cell count of 14.6 $\times 10^9$/L (normal 4.0–10.8), lactate 4.3 mmol/L (normal 0.7–2.1), haemoglobin 7.9 gm/dL (normal 11.0–14.5), sedimentation rate 66 mm/hour (normal 0–22), high-sensitivity C-reactive protein 62.6 mg/L (normal 0–3), creatinine 1.25 mg/dL (normal 0.52–1.04), albumin 2.1 g/dL (normal 3.5–5.0), total bilirubin 0.7 mg/dL (normal 0.2–1.3), alanine transaminase 26 U/L (normal 15–41), aspartate transaminase 55 U/L (normal 3–34), alkaline phosphatase 187 U/L (normal 45–117) and negative urinalysis.

The patient was admitted to the intensive care unit for presumed sepsis secondary to acute cholecystitis and was treated with aggressive fluid resuscitation and antibiotics (empiric intravenous vancomycin and piperacillin/tazobactam with subsequent addition of daptomycin and imipenem).

After haemodynamic improvement, the patient was transferred to the internal medicine floor for further care. She continued to spike fevers with intermittent tachycardia, while a rapid uptrend in her liver enzymes was noted (table 1). Examination was notable for marked jaundice, right upper quadrant tenderness and a grade II/VI systolic murmur. Ostomy site was intact with stable output.

INVESTIGATIONS

Despite extensive workup, the source of the presumed sepsis remained elusive. Ultrasonography of the right upper quadrant was notable for non-specific gallbladder wall thickening, negative sonographic Murphy sign and absence of biliary obstruction or gallstones. In contrast, hepatobiliary scintigraphy (hepatobiliary iminodiacetic acid scan) demonstrated high-grade biliary obstruction with absence of extrahepatic biliary transit of the radiopharmaceutical. CT of the abdomen and pelvis with intravenous contrast revealed oedema around the gallbladder without calcified gallstones and no evidence of abscess or Crohn's flare. Crohn's flare was further excluded via magnetic resonance enterography. The patient underwent endoscopic retrograde cholangiopancreatography with sphincterotomy, which redemonstrated a normal biliary duct system with normal intrahepatic, common hepatic and common bile ducts (the latter two measuring 2–3 mm in diameter). Opacification of the cystic duct (1 mm) and partial gallbladder opacification were noted.

Blood cultures were positive for *Peptostreptococcus* on admission, but all subsequent cultures

To cite: Patedakis Litvinov BI, Pathak AP. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-220988

Table 1 Liver function tests during the two hospitalisations and subsequent outpatient follow-up visits

	Total bilirubin(mg/dL)	AST(U/L)	ALT(U/L)	Alkaline phosphatase(U/L)
Normal ranges	0.2–1.3	3–34	15–41	45–117
First hospitalisation				
Admission	0.7	55	26	187
Day 12	11.6	342	176	1101
Discharge	2.4	96	113	717
Second hospitalisation				
Discharge	5.3	143	125	1112
Hepatology				
2-month follow-up	0.7	65	48	410
Gastroenterology				
4-month follow-up	0.8	41	41	410
Gastroenterology				
5-month follow-up	0.7	93	85	246

ALT, alanine transaminase; AST, aspartate transaminase.

revealed no growth of microorganisms. Although the patient's fevers and leucocytosis gradually resolved with antibiotic therapy, the cholestasis persisted. On hospital day 8, the patient underwent a percutaneous biopsy of the liver, which revealed numerous non-caseating granulomas with surrounding chronic inflammation, mild portal fibrosis and microsteatosis (figure 1). A percutaneous cholecystostomy tube was placed out of concern for acalculous cholecystitis; bile cultures, however, yielded no bacterial growth.

Acid-fast, fungal and Gram staining of the liver biopsy were negative for microorganisms, as were acid-fast bacilli blood cultures, urine Histoplasma antigen and serologies for hepatitides A/B/C, Epstein-Barr virus (EBV), herpes simplex virus (HSV), cytomegalovirus (CMV), HIV and rapid plasma reagin (RPR). Repeat urinalysis, cultures and echocardiography were negative. CT of the chest with intravenous contrast was normal except for two very small ground-glass nodular opacities within the upper lobe anteriorly and within the posterior basal segment of the right lower lobe (figure 2). No enlargement of mediastinal or hilar lymph nodes was noted. Pulmonary function tests were normal. Tests for antismooth muscle, antimitochondrial M2 and antinuclear antibodies were negative.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for non-caseating hepatic granulomas includes drug-induced, infectious, sarcoid-related and autoimmune aetiologies.

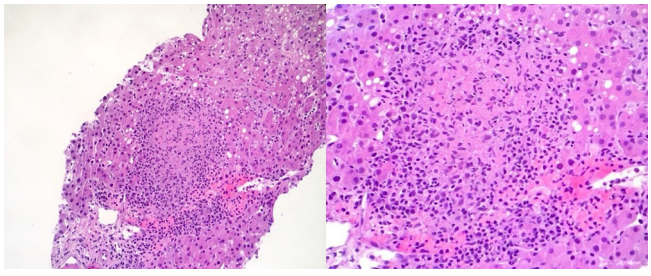

Figure 1 Patient's liver biopsy specimen showing a non-caseating granuloma (low and high magnifications). Granuloma is a circumscribed lesion that forms in response to chronic inflammation in body tissues. It consists of a central aggregation of modified (epithelioid) macrophages and a peripheral rim of lymphocytes and fibroblasts.

Infliximab has been used to treat hepatic granulomas and sarcoidosis in patients not responding to corticosteroids.[1–3] However, some authors have described a paradoxical development of granulomatous hepatitis and extrapulmonary sarcoidosis in patients treated with tumour necrosis factor alpha (TNFα) inhibitors.[4 5] The fact that our patient developed cholestasis during her hospital stay and had been off infliximab for several months prior to presentation argued strongly against a drug-associated aetiology for her liver granulomas.

The exclusion of infectious causes in symptomatic granulomatous hepatitis is crucial, since inappropriate corticosteroid therapy may promote the spread of an underlying infection. Infectious aetiologies were excluded based on the patient's clinical history, demographic characteristics, radiographic findings and infectious disease workup. Acid-fast, fungal and Gram staining of the liver biopsy were negative for microorganisms, as were acid-fast bacilli blood cultures, urine Histoplasma antigen and serologies for hepatitides A/B/C, EBV, HSV, CMV, HIV and RPR.

Autoimmune hepatitis and primary biliary cholangitis (PBC) were excluded based on the histopathological characteristics of the liver biopsy and negative antismooth muscle, antimitochondrial M2 and antinuclear antibodies. Primary sclerosing cholangitis (PSC) was ruled out based on the endoscopic retrograde cholangiopancreatography and liver biopsy findings.

CT of the chest showed no evidence of pulmonary sarcoidosis or other abnormalities, except for two small non-specific ground-glass opacities (figure 2). Pulmonary function tests were normal. Angiotensin-converting enzyme levels were not tested.

Based on the above findings, we concluded that the hepatic granulomas most likely represented either an extraintestinal

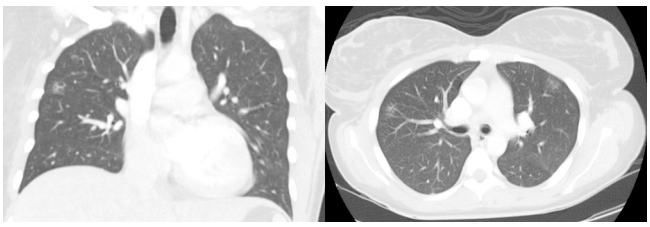

Figure 2 CT of the chest with intravenous contrast showing small ground-glass nodular opacities within the upper lobes. No pleural collections, mediastinal or hilar lymph node enlargement were noted.

manifestation of CD or an isolated extrapulmonary manifestation of sarcoidosis.

TREATMENT

Following the completion of her antibiotic course, the patient experienced a gradual improvement in her symptoms and her liver function enzymes began to downtrend (table 1). She was discharged on prednisone 40 mg and was instructed to follow-up with her CD specialist and a hepatologist.

OUTCOME AND FOLLOW-UP

The patient presented to a different local hospital 1 month later with similar sepsis-like symptoms. She was admitted and treated for presumed healthcare-acquired pneumonia based on pleuritic chest pain and new basilar opacities detected on CT, but, once again, no definite source of infection could be identified. As before, a marked elevation in liver enzymes followed by a gradual downtrend was noted. Following discharge, the patient was treated with prednisone for 2 months. Tests from subsequent visits continued to show downtrending liver markers (table 1).

DISCUSSION

Hepatic granulomas

Granuloma is a circumscribed lesion that forms in response to chronic inflammation in body tissues. It consists of a central aggregation of modified (epithelioid) macrophages and a peripheral rim of lymphocytes and fibroblasts.[6] The morphology of granulomas can be useful in refining the differential diagnosis. Four major histological variants of hepatic granulomas have been described: (1) caseating, such as those seen in tuberculosis; (2) non-caseating, as seen in sarcoidosis; (3) fibrin ring, caused by infections and vasculitides; and (4) lipogranulomas, often seen in hepatic steatosis and mineral oil ingestion. A variety of disorders can cause granulomas in the liver. In the USA, up to 75% of hepatic granulomas are associated with sarcoidosis, tuberculosis, PBC and drug reactions.[7]

The clinical manifestations of hepatic granulomas are related to their pathophysiology. Activated macrophages and lymphocytes release cytokines that may cause systemic symptoms (fever, anorexia night sweats) or direct hepatic injury. Occasionally, the finding of granulomas on liver biopsy may be the only clue to the presence of an underlying systemic disease. In most cases, however, laboratory evidence of inflammation, increased levels of alkaline phosphatase or hepatomegaly provides additional clues.[6]

The differential diagnosis of hepatic granulomas can be broadly categorised into sarcoid-related, autoimmune, drug-induced, infectious, malignant and idiopathic aetiologies. In the remaining sections, we briefly review hepatic granulomas in the context of sarcoidosis and CD.

Hepatic sarcoidosis

Despite recent advances in immunogenetic research, the exact pathogenesis of sarcoidosis remains unknown.[8 9] Virtually all (99%) sarcoid granulomas are non-caseating, accounting for up to 30% of all cases of granulomatous hepatitis.[6] Additional histopathological findings include periportal fibrosis and chronic intrahepatic cholestasis.[10] Such lesions, however, are not pathognomonic for sarcoidosis and may resemble, for example, those seen in patients with inflammatory bowel disease and PBS or PSC.[11]

Sarcoidosis is a multiorgan disorder most commonly affecting the lungs.[12] Extrapulmonary manifestations of sarcoidosis include the lymph nodes, skin, eyes and liver.[13] Isolated hepatic involvement, although well documented, remains a relatively rare finding.[10 14] Most patients with hepatic sarcoidosis are asymptomatic. The most common symptoms are abdominal pain and hepatosplenomegaly. Occasionally, the main presenting feature is elevated liver enzymes.[15–17]

Hepatic sarcoidosis is a diagnosis of exclusion, since there are no pathognomonic signs on liver biopsy that can firmly establish the diagnosis. Other causes, such as infections, autoimmune disorders, drug-induced granulomas and malignancy, must be excluded. While the lack of extrahepatic involvement does not exclude the diagnosis of hepatic sarcoidosis, a definitive diagnosis requires evidence of sarcoid lesions in at least one other organ.[18]

Asymptomatic patients with non-infectious hepatic granulomas do not require treatment. The mainstay therapy for symptomatic patients consists of corticosteroids. Relapses may occur after corticosteroid discontinuation, requiring repeat courses.[19 20] Ursodeoxycholic acid has been used to treat pruritus in patients with severe cholestasis and jaundice.[10] In patients not responding to or not tolerating corticosteroids, alternative therapies, including azathioprine, methotrexate and TNFα inhibitors, have been used successfully.[1 2]

Hepatic granulomas in CDand overlap with sarcoidosis

Hepatic granulomas are a rare complication of CD.[21] As with most hepatobiliary manifestations of CD, their presence is typically unrelated to intestinal disease activity. Patients may present with fever, hepatomegaly and elevated alkaline phosphatase levels.[22]

The prevalence of hepatic granulomas due to CD is unknown. Hilzenrat *et al*[23] reported a case of granulomatous hepatitis in a patient with CD who presented with fever and cholestasis, closely resembling our case. Reviewing the literature, they found a total of 12 biopsy-confirmed cases of hepatic granulomas associated with CD. However, a rigorous exclusion of alternative causes may not have been feasible in some of the cited studies. McCluggage and Sloan,[24] in their retrospective study of 163 liver biopsies, attributed another three cases of granulomatous hepatitis to CD.

The co-occurrence of sarcoidosis and CD is a very rare phenomenon, yet more frequent that would be expected by chance alone.[25] This observation has led to the hypothesis that there may be an etiopathogenetic link between the two disorders.[26] The coexistence of sarcoidosis and CD has been observed among different members of the same family, suggesting a possible genetic overlap.[27–29] Genetic analyses have identified Nod2/CARD15 polymorphisms in both disorders,[30] as well as common susceptibility loci on chromosome 10p12.2.[31] A shared pathogenetic mechanism is also supported by the fact that both CD and sarcoidosis tend to respond to anti-TNF therapy.[32] Clearly, further studies are needed to better understand these relationships.

In summary, the exact cause of hepatic granulomas can be difficult to ascertain. The diagnosis is particularly challenging in patients with suspected extraintestinal CD, which can mimic extrapulmonary sarcoidosis. Our case highlights some of the dilemmas that clinicians may face when treating such patients.

Contributors Both authors have contributed equally to this work, including reviewing the patient's medical records, researching relevant medical literature, and preparing and editing the manuscript. The corresponding author obtained the patient's informed consent.

Competing interests None declared.

Learning points

- Cholestasis coupled with systemic symptoms can pose a diagnostic conundrum in the setting of coexisting Crohn's disease (CD).
- Exclusion of infectious causes in symptomatic granulomatous hepatitis is crucial, since inappropriate corticosteroid therapy may promote the spread of an underlying infection.
- Hepatic granulomas are a relatively rare manifestation of both extraintestinal CD and extrapulmonary sarcoidosis.
- CD and sarcoid hepatic granulomas share several etiopathogenetic features and further research is needed to better characterise the relationship between the two overlapping disease entities.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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