CASE REPORT

An unusual cause of febrile hepatitis

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SUMMARY

We describe the case of a 51-year-old man with recently diagnosed ulcerative colitis who developed fever and elevated liver enzymes as well as cholestasis a few weeks after starting treatment with mesalazine. As no obvious cause was found and fever persisted, liver biopsy was performed and revealed granulomatous hepatitis. The patient recovered completely after cessation of mesalazine, so that a drug-induced granulomatous hepatitis after exclusion of other differential diagnoses in an extensive work up was assumed. The present case demonstrates that even though drug-induced liver injury due to mesalazine is rare, it should be considered in unclear cases and lead to prompt discontinuation of mesalazine.

BACKGROUND

Mesalazine has become an important basic drug for the treatment of inflammatory bowel disease (IBD). Whereas sulfasalazine is well known to be associated with hepatotoxicity, mesalazine-induced hepatitis is a rare condition.

CASE PRESENTATION

A 51-year-old man was admitted to our emergency department because of a 10-day course of intermittent fever that did not subside despite empirical antibiotic therapy with ciprofloxacin during the past 7 days. He suffered from a distally accentuated ulcerative colitis, which had been diagnosed by histological examination 2 months previously. Subsequently, systemic treatment with mesalazine (4 g/day) as well as topical mesalazine and budesonide was initiated. A course of prednisone was tapered until 10 days before admission. At the time of presentation, the patient reported generalised weakness as well as nausea. On further questioning, he stated that he had night sweats and fever that worsened in the evening. Incidentally, he mentioned that he remembered a single day of absent fever—a day he had accidentally forgotten to take his medication.

INVESTIGATIONS

On admission, the patient had a subfebrile temperature of 37.4°C. Blood pressure was 120/70 mm Hg and pulse 60/min. The abdomen was not tender on palpation and, likewise, the remainder of the clinical examination was unremarkable. Laboratory data disclosed an elevated C reactive protein (130 mg/L) without leucocytosis or eosinophilia, an elevated erythrocyte sedimentation rate, mild thrombocytopenia as well as elevated liver enzymes and cholestasis parameters: aspartate aminotransferase 137 U/L, alanine aminotransferase

319 U/L (normal <50 U/L), γ -glutamyltransferase 730 U/L (normal <60 U/L) and alkaline phosphatase of 385 U/L (normal range 40–129 U/L). Direct bilirubin was slightly elevated (7 μ mol/L, normal <4 μ mol/L) while the total bilirubin was within normal range. Ferritin was elevated with 1241 μ g/L (normal range 23–290 μ g/L) but transferrin saturation was normal. Blood and urine cultures were negative and a chest X-ray was unremarkable. Ultrasound of the abdomen showed slight hepatosplenomegaly but no abnormality of the biliary tract. A computed scan of the abdomen revealed a thickened distal colonic wall without acute inflammatory changes. No evidence of a recent infection with malaria, Lyme disease, hepatitis A, B, C or E viruses, Epstein-Barr virus (EBV), cytomegalovirus (CMV) or HIV was found. Antibiotic therapy was stopped on admission as there was no clear focus of infection.

Further laboratory tests showed positive antinuclear antibodies (1:320, normal <1:80), detectable perinuclear antineutrophil cytoplasmic antibodies, as well as elevated antimyeloperoxidase antibodies (5.9, normal <1.0 MOC). Anti-liver-kidney-membrane antibodies, antimitochondrial as well as antismooth muscle antibodies were negative. This constellation was discussed with an immunologist and interpreted as secondary to the known IBD. Because of the unidentified focus of fever, suspected infection as well as persistently elevated liver enzymes, liver biopsy was performed on day 8 of the patient's hospital stay.

Histological examination of a non-fragmented specimen with 18 portal fields showed non-necrotising granulomatous hepatitis with epithelioid cells and numerous eosinophils (figure 1). There was no evidence of interface hepatitis, portal lymphoplasmacytic infiltrates or piecemeal necrosis. Signs of destructive cholangitis or ductopenia in immunohistochemical staining (CK7 and CK19) were not found. Additional staining methods showed neither candida colonisation nor acid fast bacilli. A PCR specific for *Mycobacterium tuberculosis* and *Mycobacterium bovis* as well as a broad-spectrum PCR for other mycobacteria performed in liver tissue were negative.

In the course of the hospitalisation, further work up for *Bartonella henselae*, *Francisella tularensis*, *Coxiella burnetii*, *Lues* and *Leishmania*, which are all known to be associated with granulomatous hepatitis, was likewise negative.

DIFFERENTIAL DIAGNOSIS

Granulomatous hepatitis is a rare condition that can be associated with systemic infections, malignancy, autoimmune disorders and drugs.¹ The main

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Figure 1 (A) Hepatic lobule with non-necrotising epithelioid granulomas (arrows). (B) Hepatic lobule with non-necrotising epithelioid granuloma with giant cell (*) and numerous eosinophils (arrow).

biochemical abnormality is a rise of the cholestatic enzymes. Fever is the most common clinical symptom.

Our initial differential diagnosis of the patients' fever included an infection. Infections causing granulomatous hepatitis can be bacterial (such as tuberculosis, other mycobacteria, brucellosis, listeriosis, tularaemia, yersiniosis and cat scratch fever) or viral (CMV, EBV and hepatitis A, B, C). Also, fungal infections such as histoplasmosis, coccidioidomycosis, *Cryptococcus*, nocardiosis and candidiasis can be rare causes of granulomatous hepatitis. Further uncommon pathogens may be parasites (toxoplasmosis, schistosomiasis, larva migrans and leishmaniasis), rickettsia (*Coxiella burnetii*) or spirochetes (secondary syphilis).^{2 3}

Cholelithiasis is common, but structural causes of the elevated liver enzymes and cholestasis were excluded with computed tomography and abdominal sonography. Moreover, there was no sign of malignancy.

A diagnosis of autoimmune hepatitis (AIH) can be performed with a combination of clinical, laboratory and histological findings. A number of specific antibodies (ANA, anti-smooth muscle antibodies, anti-smooth muscle antibody, soluble liver antigen, liver kidney microsomal antibody) are of use and liver biopsy is mandatory. AIH is a rare cause of hepatic granulomas. As both serum IgG and serum electrophoresis as well as the score for AIH were normal, we did not favour this diagnosis.

Further, disorders of the hepatobiliary system arise frequently as extraintestinal manifestations of IBD. In patients with ulcerative colitis, primary sclerosing cholangitis (PSC), a chronic fibroproliferative disorder of the biliary tree, is commonly seen.⁴ This diagnosis is based on characteristic bile duct changes with multifocal strictures and segmental dilations.

Furthermore, in PSC, the autoantibodies most frequently reported are antinuclear antibody (ANA) and perinuclear anti-neutrophil cytoplasmic antibodies—which were both found in our patient. Histological findings showed no indicative findings for an associated PSC (eg, ductopenia) and a magnetic resonance cholangiopancreatography in the follow-up months later showed completely normal findings.

Other cholestatic disorders, such as primary biliary cirrhosis (PBC), were also deemed unlikely. PBC without presence of antimitochondrial antibodies and detection of only non-specific ANAs, as seen in our patient, is uncommon but possible. The clinical presentation—especially the lack of pruritus—along with the patients' demographics and the absence of destructing cholangitis in histology, did not fit this diagnosis.

Sarcoidosis is another differential diagnosis of granulomatous hepatitis. Our patient had no evidence of extrahepatic

manifestations of sarcoidosis (eg, cutaneous manifestations) or chest X-ray abnormalities. Therefore, this diagnosis seemed unlikely.

Drug-induced liver injury as well as 'drug fever' are important clinical considerations but remain a diagnosis of exclusion, with countless medications implicated. Liver biopsy can contribute to diagnostic accuracy. Common drugs associated with liver granulomas are allopurinol, aspirin, carbamazepine, diltiazem, nitrofurantoin, penicillin, phenytoin, quinidine and sulfa drugs.⁵

Our patient had a course of antibiotic therapy with ciprofloxacin. According to the literature, ciprofloxacin usually causes cholestatic hepatitis.⁶ In our patient, the deterioration of liver function after discontinuation of ciprofloxacin made a direct causality unlikely. In addition, granulomas are not typical of ciprofloxacin toxicity, whereas sulfa drugs may precipitate granuloma formation. For these reasons, we felt ciprofloxacin was unlikely to be the causative agent for the granulomatous hepatitis.

TREATMENT

On the day of the liver biopsy, the patient omitted his medication as he was asked to fast before the intervention. On that day, no fever was documented.

He recalled also not having had fever on a day he had previously forgotten to take his medication.

Mesalazine was therefore discontinued, following which the patients' fever resolved completely and the liver enzymes declined (figure 2). In addition, we administered a tapered course of steroids over 6 weeks (initial dose of prednisone 40 mg/day) to treat the granulomatous hepatitis.

OUTCOME AND FOLLOW-UP

Liver enzymes as well as inflammatory signs in the blood normalised after mesalazine was stopped.

A systemic rechallenge with mesalazine was not performed to avoid harming the patient. As his ulcerative colitis required long-term treatment after another relapse, he received mesalazine suppositories 3 months later. Without steroid therapy, the patient continued to do well under suppository therapy. Liver enzymes during a follow-up of overall 12 months remained within the normal range.

DISCUSSION

This case report describes a patient with ulcerative colitis who developed biopsy-proven hepatic injury following systemic therapy with mesalazine.

Figure 2 Evolution of temperature and biological parameters.

Mesalazine is a commonly prescribed medication in the treatment of IBD, particularly ulcerative colitis. Along with other 5-aminosalicylic acids, it was developed as an alternative agent to sulfasalazine, which was poorly tolerated by many patients and caused allergic reactions. Its mechanism of injury as well as mechanism of action are not clearly understood.⁷

Adverse drug reactions have formerly been attributed mainly to the sulfasalazine moiety. Although mesalazine preparations are generally well tolerated, adverse reactions such as worsening colitis, renal toxicity (eg, interstitial nephritis), pulmonary toxicity and pancreatitis have been described in the past years.⁸

There are different mechanisms by which drugs can be hepatotoxic, besides direct toxicity, there are idiosyncratic reactions. In contrast to sulfasalazine, there are only a few published cases of mesalazine-induced liver injury, and these include cholestasis⁹ as well as severe hypersensitivity.¹⁰

In 1999, the first case report was published describing biopsy-proven granulomatous hepatitis associated with mesalazine.¹¹ Up until then, this condition was attributed only to sulfasalazine therapy, and withdrawal of the drug led to a total recovery—in most cases without additional measures.^{12–14}

One case report¹⁵ describes possible immune-mediated late liver toxicity of mesalazine in a patient with persistent liver dysfunction (transaminases $>10\times$ ULN) who had taken mesalazine for 21 months. Liver biopsy showed chronic hepatitis lesions but without granuloma. The patient had raised serum IgG levels as well as antinuclear and antismooth muscle autoantibodies. After stopping mesalazine and without any immunosuppressive therapy, liver enzymes and serum IgG became normal and autoantibodies disappeared. The liver disease never relapsed.

As mentioned above, hepatic disease is common in patients with IBD. In our patient, other aetiologies of hepatitis and fever were considered but ruled out, making the diagnosis of drug-induced liver injury plausible. We are aware of the fact that the patients' initial presentation with fever coincided with the cessation of a course of steroids. Possibly, the steroid therapy, which the patient had received because of a colitis flare, disguised an already existing liver injury.

According to the literature, drug fever resolves within 72–96 h after discontinuing the offending drug. In the above mentioned case report of mesalazine-induced granulomatous hepatitis,¹¹ the fever disappeared within 3 days (both on initial cessation as well as after rechallenge). We noticed a faster decline, but this may have been a coincidence.

Physicians may be tempted to continue mesalazine during a flare of IBD. However, as mesalazine itself can cause serious liver injury, continuation of the drug may further worsen the

clinical course. As chronic liver damage can develop, it is of the utmost importance that adverse drug reactions are routinely considered in a patient with persistent fever and clinical deterioration despite standard treatment.

Learning points

- Consider that mesalazine is a potential cause of unexplained fever in patients with inflammatory bowel disease and no focus of infection.
- As soon as liver dysfunction occurs, mesalazine administration should be discontinued to prevent permanent liver damage.
- A careful history and review of all medication is crucial.
- Recognition of drug fever is challenging but clinically important.

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Competing interests None declared.

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