CASE REPORT

Acute hepatitis in a young woman with systemic lupus erythematosus: a diagnostic challenge

Rita Barosa, Lúcia Roque Ramos, Cristina Fonseca, João Freitas

Department of Gastroenterology,
Hospital Garcia de Orta,
Almada, Portugal

Correspondence to

Dr Rita Barosa,
a.rita.b@gmail.com

SUMMARY

A 48-year-old woman with systemic lupus erythematosus diagnosis was on naproxen, hydroxychloroquine and acetylsalicylic acid. She had self-suspended all medication and resumed 1 year later. Five days after the medication was resumed, she developed acute hepatitis, with biochemical hepatic cytolysis, hypergammaglobulinaemia and a serum antinuclear antibody titre of 1/2560. Idiopathic autoimmune hepatitis was considered, but drug-induced liver injury could not definitely be ruled out. Patient declined liver biopsy. Oral prednisolone was started. Within 3 months with prednisolone being tapered to 10 mg/day, a new flare occurred. Liver biopsy was performed and it favoured autoimmune hepatitis diagnosis. We discuss the diagnostic options and treatment approach in a patient with autoimmune disease and possible drug-induced liver injury who initially declined liver biopsy.

BACKGROUND

Acute hepatitis is a frequent condition and may evolve to acute liver failure which is associated with significant mortality. Specific treatment is sometimes indicated as in autoimmune hepatitis, thus establishing the underlying cause is important.

In industrialised countries where polymedication is frequent, drugs are the most commonly identified causes of acute liver failure and autoimmune hepatitis (AIH) presenting as acute liver failure is uncommon.¹

Autoimmune or drug-induced hepatitis have no pathognomonic features and both require the exclusion of other aetiologies; thus, defining a drug or toxin as the cause of acute hepatitis in a patient with an autoimmune disease poses a diagnostic challenge.

CASE PRESENTATION

We report a 48-year-old woman with a history of systemic lupus erythematosus (SLE) manifested predominantly by arthritis and antiphospholipid antibody syndrome who was daily medicated with 6 mg of deflazacort, 400 mg of hydroxychloroquine, 150 mg of acetylsalicylic acid and 1000 mg maximum of naproxen for 15 years. The patient had self-suspended medication 1 year before and resumed all medication 5 days before hospital admission. She had nausea and anorexia, and 3 days later jaundiced sclera was noticed. She denied fever, diarrhoea, pruritus, recent trips, any history of alcohol or recreational drug use or exposure to other xenobiotics, including herbal or dietary supplements. She had normal vital signs

and no signs of encephalopathy. A jaundiced skin was evident, but without bruising or haemorrhagic lesions. Her cardiopulmonary examination was normal. The abdominal examination failed to disclose liver or spleen enlargement, and there were no signs of ascites. No enlarged lymph nodes were found and there was no peripheral oedema.

INVESTIGATIONS

Haematological investigations revealed no eosinophilia or anaemia. Biochemical tests demonstrated elevated aminotransferases (AST 1270 (normal <38 U/l), ALT 1740 (normal <40 U/l)), direct hyperbilirrubinaemia (total bilirubin 11.8 (normal <1.2 mg/dl), direct bilirubin 9.9 (normal <0.3 mg/dl)), normal γ -glutamyl transferase (GGT) and slightly elevated alkaline phosphatase (ALP 175 (normal 40–129 U/l)) with ALT to ALP ratio of 9. The prothrombin time was prolonged (19.4/11.5 s). Protein electrophoresis revealed polyclonal hypergammaglobulinaemia with predominant increase in IgG (2.72 (normal 0.66–1.50 mg/dL)). Serum ceruloplasmin, iron and ferritin levels were normal. Antibody screening tests for hepatitis A, B and C and serology for Cytomegalovirus, Epstein-Barr and Herpes virus were all negative. Serum antinuclear antibody (ANA) was highly positive (1/2560), anti-mitochondrial antibody (AMA) was 1/20, anti-smooth muscle (SMA) and anti-liver-kidney microsome type 1 (anti-LKM1) antibodies were both negative. Hepatic ultrasonography revealed a slightly enlarged liver and no findings suggestive of chronic liver disease. Liver biopsy was declined by the patient.

International autoimmune hepatitis score before treatment showed probable AIH.

DIFFERENTIAL DIAGNOSIS

High titres of ANA, hypergammaglobulinaemia with predominant increase in IgG and the presence of SLE suggest autoimmune aetiology. Some forms of drug-induced hepatotoxicity may also present with autoimmune laboratory and histological features. However, ANA is present in 98% of SLE patients,² hypergammaglobulinaemia is frequent in those patients and other autoantibodies which may also be present in AIH were absent. Recognition of underlying cause is important since steroid therapy significantly improves prognosis in acute and severe AIH.³

TREATMENT

Based upon the possibility of drug-induced liver injury (DILI), N-acetylcysteine was initiated. There

To cite: Barosa R, Ramos LR, Fonseca C, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-008591

was an increased prolonged prothrombin time (21.4/11.5 s) with AST greater than 10 times the upper limit of normal, which are absolute indication for treatment of AIH. Oral prednisolone monotherapy was started, despite the lack of knowledge of the precise nature of the hepatic changes was not already established.

OUTCOME AND FOLLOW-UP

There was prompt improvement of liver enzyme values and prothrombin time normalised after prednisolone has been started. Patient was asymptomatic and discharged from the hospital 12 days later.

On the third month of follow-up with prednisolone tapering to 10 mg/day and no drug introduced there was a clinical and laboratorial relapse with elevated aminotransferases and bilirubin, with no changes in prothrombin time or cholestasis. Liver biopsy was performed showing necroinflammatory activity with hepatocellular regeneration reflected by rosette formation and interface hepatitis with mononuclear cell infiltrate (figure 1).

DISCUSSION

There are no pathognomonic features for the diagnosis of AIH and drug-induced acute hepatitis diagnosis might be challenging due to the absence of specific laboratory markers and the inability to rechallenge the patient. Both conditions are diagnosis of exclusion: metabolic, viral and cholestatic liver disease were ruled out.^{4 5}

Approximately 5% of all cases of jaundice occurring in adults are ascribed to drugs.⁶ Consumption of nutritional supplements or herbal agents was excluded. Idiosyncratic reaction is the most frequent pathway of DILI and usually occurs 3–4 weeks after the intake of the substance, but may occur after several months of use, although it is unlikely that a drug used for 1–2 years would lead to liver damage *de novo*.⁷ There may exist an underlying immune process presenting with fever, rash, arthralgias, eosinophilia and haemolytic anaemia. As occurs in autoimmune hepatitis, hypergammaglobulinaemia, autoantibodies or plasma cell infiltration on liver biopsy may also be present. Liver injury usually resolves after offending agent is ceased and new exposure is followed by rapid and potentially dangerous clinical deterioration. Our patient discontinued all potentially offending drugs, which is the most important therapeutic measure in DILI.⁸

Figure 1 Liver biopsy (A) Lymphoplasmacytic portal inflammatory infiltrates with interface activity, lobular infiltrate and some eosinophiles (arrow). (B) Acidophilic (apoptotic) bodies.

N-acetylcysteine was started based on its possible benefit in non-acetaminophen-related acute liver failure, as proposed by some authors.⁹

In DILI, laboratory values may reveal a hepatocellular, cholestatic or mixed liver injury. Our patient presented with hepatocellular injury pattern characterised by ALT more than two times the upper limit of normal, slightly elevated ALP and ALT:ALP ratio greater than 5. Unfortunately, there is no histological pattern of injury specific for toxic liver damage⁷; although some agents may produce a definite histological findings, the same substance under different conditions may cause different histological patterns.¹⁰ There is also an overlap of histological findings for AIH and DILI; however, sufficient differences exist so that the pathologists can often use the pattern of injury to suggest the correct diagnosis.¹⁰

A possible individual susceptibility, female gender, age, exposure to multiple drugs and underlying autoimmune disease are risk factors present in our patient for drug-induced idiosyncratic reaction.⁸

In patients with rheumatic disease, the combination of two or more hepatotoxic drugs increases DILI risk by a factor of 6.¹¹ Seven cases of naproxen-induced liver injury have been reported in the English literature and histopathological changes range from acute hepatitis, bridging necrosis and/or cholestasis.¹² Acetylsalicylic acid hepatotoxicity was first described about 30 years ago, but its occurrence is currently very low.¹³ Although there is evidence of increased risk of acetylsalicylic acid liver damage in rheumatic patients,¹³ its toxicity is considered to be dose dependent and our patient was under low dose of acetylsalicylic acid. No hydroxychloroquine-induced liver injury is consistently reported.

Patients with AIH are about four times more often women and there is a bimodal age distribution between 10–20 and 45–70 year-old in type 1 AIH (the most frequent type).¹⁴

AIH laboratory diagnosis is based on the demonstration of autoantibodies in serum, but in up to 13% of patients no autoantibodies are found.¹⁵ Aminotransferase levels in serum are markedly elevated while markers of cholestasis are normal or slightly increased, as occurred in our patient.¹⁶ Although the microscopic findings are not disease specific, liver biopsy is the most useful diagnostic tool, and together with clinical evolution allowed the diagnosis of AIH.¹⁰

Up to 50% of patients with AIH present extrahepatic immune-mediated diseases such as SLE.¹⁶ About 8–23% of SLE patients have hepatic involvement being hepatotoxic drugs and viral hepatitis the most relevant causes.¹¹ About 29% of those patients have no other cause than SLE for hepatic changes,¹¹ but whether AIH- and SLE-associated hepatitis are two distinct entities remains controversial. It is challenging to define the definite role of medication in our patient's liver injury.

Although controlled studies are lacking, selected patients with severe hepatotoxicity and autoimmune features as discussed above may benefit with steroid therapy, especially if there is no recovery within 1–2 weeks after discontinuing the offending agent or if there is evidence of liver failure.¹⁷

Since there is a heterogeneous clinical presentation for AIH, a scoring system that includes typical and less characteristic criteria has been proposed to help in AIH diagnosis.¹⁸

Autoantibodies could not make a differential diagnosis of AIH and SLE serological features and some studies have questioned the use of AIH score among patients of SLE.¹⁹ It is not expected for autoantibodies to become negative in a patient with SLE as may occur in DILI with autoimmune features after the offending agent is ceased.

As often occurs, liver biopsy was not initially possible and prednisolone withdrawn with careful follow-up helped differentiating idiopathic AIH which typically relapses without immunosuppression, from DILI with autoimmune features.¹⁷

Learning points

- ▶ Autoimmune hepatitis (AIH) and drug-induced liver injury (DILI) are both diagnosis of exclusion.
- ▶ Drugs and viral hepatitis are the most common causes of hepatic changes in SLE patients, but 29% of those patients have no other cause than SLE for the hepatic changes.
- ▶ AIH diagnosis may be challenging as there are no pathognomonic features and autoantibodies are absent in up to 13% of AIH cases.
- ▶ There is also no typical presentation or histology for drug-induced hepatotoxicity and new exposure to offending substance may trigger dangerous acute liver failure.

Acknowledgements We would like to thank Dr Joana Nogueira, Dr Jorge Oliveira e Neta, and Dr Maria José Brito (Department of Pathology), who performed the histological diagnosis and image selection.

Contributors All authors contributed equally to manage the case and participated in drafting and critical revision of the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Khashab M, Tector AJ, Kwo PY. Epidemiology of acute liver failure. *Curr Gastroenterol Rep* 2007;9:66–73.
- 2 Tan EM, Cohen AS, Fries JF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
- 3 Czaja AJ. Current and future treatments of autoimmune hepatitis. *Expert Rev Gastroenterol Hepatol* 2009;3:269–91.
- 4 Al-Khalidi JA, Czaja AJ. Current concepts in diagnosis, pathogenesis and treatment of autoimmune hepatitis. *Mayo Clin Proc* 2001;76:1237–52.
- 5 Lee WM. Drug-induced hepatotoxicity. *N Engl J Med* 1995;333:1118–27.
- 6 Bjor M, Poupon R, Grangé JD, *et al.* Drug-induced hepatotoxicity. The 13th updated edition of the bibliographic database of drug-related liver injuries and responsible drugs. *Gastroenterol Clin Biol* 2000;24:1052–91.
- 7 Gunawan BK, Kaplowitz N. Mechanisms of drug-induced liver disease. *Clin Liver Dis* 2007;11:459–75.
- 8 Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an overview. *Expert Opin Drug Saf* 2007;6:673–84.
- 9 Lee WM, Hynan LS, Rossaro L, *et al.* Intravenous N-acetylcysteine improves transplant free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009;137:856–64.
- 10 Suzuki A, Brunt EM, Kleiner DE, *et al.* The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis vs. drug-induced liver injury. *Hepatology* 2011;54:931–9.
- 11 Soultati A, Dourakis S. Hepatic manifestations of autoimmune rheumatic diseases. *Ann Gastroenterol* 2005;18:309–24.
- 12 Ali S, Pimentel JD, Ma C. Naproxen-induced liver injury. *Hepatobiliary Pancreat Dis Int* 2011;10:552–6.
- 13 Bessone F. Non-steroidal anti-inflammatory drugs: what is the actual risk of liver damage? *World J Gastroenterol* 2010;16:5651–61.
- 14 Schaefer EA, Pratt DS. Autoimmune hepatitis current challenges in diagnosis and management in a chronic progressive liver disease. *Curr Opin Rheumatol* 2012;24:84–9.
- 15 Czaja AJ, Carpenter H, Santrach P, *et al.* The nature and prognosis of severe cryptogenic chronic active hepatitis. *Gastroenterology* 1993;104:1755–61.
- 16 Manns MP, Strassburg CP. Autoimmune hepatitis: clinical challenges. *Gastroenterology* 2001;120:1502–17.
- 17 Czaja AJ. Drug-induced autoimmune-like hepatitis. *Dig Dis Sci* 2011;56:958–76.
- 18 Alvarez F, Berg PA, Bianchi FB, *et al.* International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999;31:929–38.
- 19 Iwai M, Harada Y, Ishii M, *et al.* Autoimmune hepatitis in a patient with systemic lupus erythematosus. *Clin Rheumatol* 2003;22:234–6.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow