CASE REPORT

Autoimmune hepatitis in a teenage boy: 'overlap' or 'outlier' syndrome—dilemma for internists

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SUMMARY

An 18-year-old boy presented with upper gastrointestinal bleeding and jaundice. Investigations revealed coarse hepatomegaly, splenomegaly and advanced oesophageal varices. Blood reports showed marked rise of alkaline phosphatase and more than twofold rise of transaminases and IgG. Liver histology was suggestive of piecemeal necrosis, interphase hepatitis and bile duct proliferation. Antinuclear antibody was positive in high titre along with positive antismooth muscle antibody and antimitochondrial antibody. The patient was positive for human leukocyte antigen DR3 type. Although an 'overlap' syndrome exists between autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC), a cholestatic variant of AIH, a rare 'outlier' syndrome could not be excluded in our case. Moreover, 'the chicken or the egg', AIH or PBC, the dilemma for the internists continued. The patient was put on steroid and ursodeoxycholic acid with unsatisfactory response. The existing international criteria for diagnosis of AIH are not generous enough to accommodate its variant forms.

BACKGROUND

Stricter the diagnostic criteria of autoimmune hepatitis (AIH) became more the most variant forms of AIH, were either casually discarded as unrelated disease entities or forcibly submerged into classic forms. The variant syndromes may represent the prelude to a hybrid disorder with a heterogeneous phenotype. Overlapping features of primary biliary cirrhosis (PBC) in a patient of AIH is a rare experience. This can either be another concurrent autoimmune disease in a susceptible host or a continuous spectrum of single autoimmune disease. It is prudent to search for coexistence of PBC in patients of AIH and vice versa because together they may lead to progressive liver disease and cirrhosis despite immunosuppressive therapy. Chronic cholestatic liver disease is a diagnostic challenge and its association with AIH in a male teenager is very uncommon. Authors have also tried to explain the genetic susceptibility of the patient by human leukocyte antigen (HLA) serotyping.

CASE PRESENTATION

An 18-year-old male student presented with one episode of massive haematemesis followed by malena for seven days. There was no history of fever, abdominal pain, swelling of body, itching or any neuropsychiatric abnormality or hepatotoxic drug intake. Though there was a history of yellowish discolouration of eyes and urine 1 year ago, at present the patient had no alteration of urine habit.

No previous blood transfusion was given and no significant family history was present. He never ingested alcohol and denied any high-risk behaviour. Physical examination showed significant pallor, mild icterus, grade II clubbing and tender gynaecomastia. Systemic examination revealed firm hepatomegaly with a liver span of 12 cm and moderate splenomegaly. No ascites or prominent abdominal vein could be appreciated. Diminished secondary sexual characters are noted. Remainder of systemic examination was within normal limit.

INVESTIGATIONS

Haematological investigation showed microcytic hypochromic anaemia (haemoglobin 4 g/dl), leucocytosis with normal neutrophil-lymphocyte ratio and adequate platelet count. His erythrocyte sedimentation rate (ESR) was 155 mm at the end of the first hour and direct Coombs' test was negative. Liver function test revealed total bilirubin 4 mg/dl with conjugated bilirubin 3.1 mg/dl, aspartate transaminase (AST) 95 U/l (normal 8–38 U/l), alanine transaminase (ALT) 80 U/l (normal 6–40 U/l), serum alkaline phosphatase (ALP) 1690 U/l (normal 98–259 U/l), γ -glutamyl transferase 221 U/l (normal 11–50 U/l), serum albumin 2.1 g/dl and globulin 5.6 g/dl. Serum protein electrophoresis showed M band in globin region. Direct estimation of serum immunoglobulin by nephelometry revealed IgG 3800 mg/dl (normal 700–1600 mg/dl) with IgG4 level of 92 mg/dl (normal 8–140 mg/dl) and IgM 480 mg/dl (normal 40–230 mg/dl). Prothrombin time was 16.8 s (control 11.2 s and international normalised ratio was 1.5). Renal function, electrolyte and glycaemic status were within normal limits. Ultrasonography of the abdomen suggested hepatomegaly with heterogeneous echotexture and gently lobulated margin. No feature of mechanical biliary obstruction was noted. Portal vein diameter was 12.5 mm with normal flow pattern. Spleen was 16.6 cm with splenic vein measuring 7.5 mm at hilum. Upper gastrointestinal endoscopy revealed extensive oesophageal varices and congested antral mucosa. Markers for hepatitis B, C and HIV infection were negative. Workup for Wilson's disease was also unremarkable. Liver biopsy was performed and histological examination found effacement of normal lobular architecture (figure 1), broad bands of fibrous tissue enclosing islands of hepatocytes forming nodules (figure 2), lymphocytic piecemeal necrosis characterised by interphase hepatitis (figure 3) and proliferation of bile ducts with intrahepatic cholestasis (figure 4). Antinuclear antibody (ANA) was positive in 1:320 titre (speckled pattern),

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Figure 1 Light microscopy of hepatic parenchyma showing effacement of normal lobular architecture and broad bands of fibrous tissue enclosing islands of hepatocytes forming regenerating nodules (H&E, original magnification $\times 50$).

antimitochondrial antibody (AMA-E2) was positive in 1:20 titre and antismooth muscle antibody (ASMA) was positive in 1:20 titre. Antibody to liver-kidney-muscle antigen (anti-LKM1 antibody) and anti-double-stranded DNA (anti-dsDNA) antibody were negative. α -1-Antitrypsin measured 269 mg/dl (normal 90–260 mg/dl).

DIFFERENTIAL DIAGNOSIS

- ▶ AIH and PBC overlap syndrome
- ▶ AIH—cholestatic variant
- ▶ PBC
- ▶ Autoimmune sclerosing cholangitis
- ▶ AIH and primary sclerosing cholangitis (PSC) overlap syndrome

TREATMENT

The patient was resuscitated with transfusion of three units of packed red cells. Endoscopic band ligation was performed and

Figure 2 Light microscopy of hepatic parenchyma showing (A) broad bands of fibrous tissue enclosing islands of hepatocytes (Reticulin stain, original magnification $\times 100$); (B) extensive periportal fibrosis (Van Gieson's stain, original magnification $\times 50$).

Figure 3 Light microscopy of hepatic parenchyma showing interphase hepatitis characterised by lymphoplasmacytic infiltration of portal tract (red arrow). Proliferation of bile duct is also noted (H&E, original magnification $\times 100$).

propranolol was given for secondary prophylaxis of variceal bleeding. Since the patient showed coexisting biochemical and histological features indicative of both AIH and PBC, prednisolone (40 mg/day) and ursodeoxycholic acid (UDCA) both were initiated along with calcium and vitamin D supplementation.

OUTCOME AND FOLLOW-UP

On follow-up after 6 weeks the patient was clinically stable with haemoglobin level 11 g/dl and ESR 66 mm at the end of the first hour, total serum bilirubin 2.8 mg/dl, conjugated bilirubin 1.8 mg/dl, ALP 699 U/l, AST 45 U/l and ALT 38 U/l. A normal MR cholangiopancreatography excluded the possibility of small duct PSC. Antibody to thyroid peroxidase, rheumatoid factor and anti-SSA, anti-SSB antibody were negative. HLA typing of the patient was positive for human leukocyte antigen DR3 type (HLADR3).

The boy presented 3 months later to the emergency department with an episode of partial seizure with secondary generalisation. Examinations found jaundice, ascites, severe weight loss and muscle wasting. Total bilirubin was 4.8 mg/dl, conjugated bilirubin 2.8 mg/dl, AST 110 U/l, ALT 92 U/l and ALP was 1632 U/l. Since the last visit, 6 months after diagnosis, though

Figure 4 Light microscopy of hepatic parenchyma showing (A) swollen hepatocytes. Proliferation of bile ducts and bridging fibrous bands are visible along with dense infiltration by inflammatory cells. (H&E, original magnification $\times 100$); (B) sinusoidal dilation and intrahepatic cholestasis is seen (red arrow). Necroinflammatory lesions are present (H&E, original magnification $\times 400$).

there is moderate rise of liver enzymes, the boy is clinically stable. The patient is maintained on UDCA and low-dose steroid.

DISCUSSION

AIH is a form of chronic hepatitis characterised by raised immunoglobulins, autoantibodies and periportal inflammation which primarily responds to immunosuppression.¹ Although it has been recognised since 1950, the term AIH was first coined by Mackay in 1965 and globally accepted by the International AIH group in 1993.^{2–4} The annual incidence of AIH is 8.5 cases in a million with female preponderance.⁵ A good number of AIH patients either share features of PBC, PSC or chronic viral hepatitis ('overlap syndromes') or have findings that are inconsistent with the diagnosis of autoimmune ('outlier syndromes').⁶ Moreover 'sequential syndromes' characterised by transitions from PBC to AIH or vice versa have also been described.⁷

Serologically AIH can be of three subtypes predominantly associated with ANA, anti-LKM1 antibody and antibody to soluble liver antigen, respectively.⁸ It is important to note that low titre of AMA can be present in 20% cases of AIH.⁹ ANA and ASMA arise in 35% and 66% of patients, respectively, with PBC.¹⁰ Anti-dsDNA antibody is seen to be present in 47% cases of AIH-PBC overlap syndrome but it was absent in our case.¹¹ Biliary changes can occur in autoimmune hepatitis in the form of bile ductular destruction or lymphocytic infiltration which constitute a cholestatic 'outlier' variant of AIH and diagnostic scores for AIH was lower in patients with bile duct changes.¹²

A low pretreatment score in our case according to the scoring system proposed by the International AIH group denied even a probable diagnosis of AIH whereas he was attributed a score of seven according to the Simplified Scoring System (2008) which ensures a diagnosis of type I AIH.^{13–14} It is worth mentioning that the scoring system for AIH was stringently adjusted to allocate greater weight against PBC and thus overlooked the cholestatic 'outlier' variant as well as the 'overlap' syndromes which are not uncommon but underestimated.¹⁵ In AIH-PBC overlap syndrome, expression of AMA and florid bile duct injury will be found in a majority of the cases whereas in cholestatic variant of AIH, AMA negativity and mere intrahepatic cholestasis will be found. However, AIH-cholestatic variant and AIH-PBC overlapping syndrome are believed to be different spectrums of same autoimmune diseases of liver leading to cirrhosis. Our case fulfils the criteria for the diagnosis of AIH-PBC overlap syndrome provided by Chazouilleres *et al*¹⁶ which is also adopted by the European Association for the Study of the Liver (EASL).

The occurrence of seizure was probably because of hepatic encephalopathy owing to severe decompensated cirrhosis in the teenage boy. Our patient expressed HLADR3 which is not only over-represented in men with type I AIH, but is also associated with a severer disease pattern with an early onset, lesser extrahepatic manifestation and minimal response to steroids.¹⁷ As no randomised controlled therapeutic trials have been carried out so far our case was treated with both steroid and UDCA according to EASL guidelines.¹⁸ An alternative approach is to start with UDCA alone and if the biochemical response is not adequate corticosteroid therapy can then be supplemented.¹⁹ Budesonide is an emerging treatment option for patients with AIH and has also been used with success in some cases of PBC-AIH overlap syndrome.²⁰

Learning points

- ▶ Histological evidence of biliary lesion in patients with autoimmune hepatitis (AIH) may reflect exuberant immune-mediated response or expressions of a variant syndrome.
- ▶ Patients with primary biliary cirrhosis (PBC)-AIH overlap syndrome show more severe disease with worse clinical outcomes compared with patients with isolated AIH or PBC.
- ▶ Patients with PBC or AIH must be screened and followed up for sequential development of AIH-PBC overlap syndrome.

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