CASE REPORT

Severe transaminitis in a paediatric patient with systemic lupus erythematosis and a discussion of the literature

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SUMMARY

A 15-year-old African-American girl with known systemic lupus erythematosis (SLE) presented to the emergency room with fever, abdominal distension, pain and vomiting. She was found to have severe transaminitis on laboratory examination, which prompted further work up including imaging and liver biopsy. Although complete diagnostic criteria were not met, histology was suggestive of autoimmune hepatitis (AIH). She was treated with steroids and azathioprine with good response and resolution of liver function tests. Availability of the literature discussing patients of any age with SLE and AIH is minimal, and consists mostly of small case series and some case reports. The juvenile literature on SLE and AIH occurring in the same patient is even scarcer and should be further studied at a multicentre level.

BACKGROUND

Autoimmune hepatitis (AIH) is a relatively uncommon chronic hepatitis that affects females 3.6 times more than males.^{1 2} It can affect any age group, gender and ethnicity; the trigger is unknown.^{1 2} It is usually characterised by serological markers as well as histological evidence of inflammatory changes.³ AIH is a diagnosis of exclusion. It is not characterised by any one particular feature, rather, it is a constellation of symptoms.¹ If untreated, AIH can progress to severe liver damage requiring transplantation.²

AIH is normally categorised as type 1 or 2.⁴ Type 1 is characterised by an adult predominance and presence of anti-smooth muscle (SMA), anti-nuclear (ANA) and/or anti-soluble liver antigen/liver-pancreas (SLA/LP) antibodies. Type 2 is found more commonly in children and has anti-liver-kidney microsome (LKM) antibodies.^{4 5} Not all cases of AIH are autoantibody positive. Up to 20% of patients with AIH may be autoantibody negative but can develop autoantibodies at a later stage.^{5 6} Autoantibody-negative AIH has been described in a small number of adults, and even more rarely in paediatrics.⁴

The International Autoimmune Hepatitis Group (IAIHG) created diagnostic criteria for scientific purposes in 1993, which were simplified in 2008 to serve as a more useful clinical tool. The simplified criteria use a point system to assign value to the important serological markers of autoantibodies and immunoglobulins, a triad of histological features from a liver biopsy as well as the proven

absence of viral hepatitis.⁷ Specifically, serological markers of AIH can include hypergammaglobulinaemia in addition to the elevated transaminases and autoantibodies aforementioned.⁴ The triad of histological features most typical of AIH include a portal lymphocytic/lymphoplasmacytic infiltrate that may extend into the lobule, emperipolesis (where inflammatory cells penetrate through the hepatocytes¹) and hepatic rosette formation ('clusters of reactive hepatocytes surrounded by inflammatory cells').^{1 7} These criteria have been validated in children, except in the case of fulminant hepatic failure.⁸

AIH must be recognised promptly and treatment initiated immediately with immunosuppressive therapy to prevent any further fibrosis, cirrhosis and/or severe liver damage.⁴ Untreated AIH has a 5-year survival of 50% and 10-year survival of 10%.⁹ Even when treated, children with AIH have a 67–87% chance of 5-year survival with their native liver.¹ While there is a degree of hepatic involvement in systemic lupus erythematosis (SLE) as well, there are not many reported cases of SLE and AIH existing in the same patient.

SLE is a multisystem autoimmune disease that has dermatological, renal, cardiovascular, musculoskeletal, haematological and, sometimes, hepatic manifestations.^{10 11} A minimal elevation of 2-fold to 3-fold increase in transaminases is seen in SLE, but this can go as high as 10-fold in the most severe cases.³

SLE and AIH have been known to coexist in a few small case series of adult patients and scattered paediatric case reports but, overall, the data are limited. In the past, there has been debate about whether or not SLE hepatitis is a separate entity from liver dysfunction in AIH, however, more and more evidence has shown that these two diagnoses are in fact distinct aetiologies, each with the potential to have very different outcomes if not treated appropriately, especially in the case of AIH. In this report, we will describe the case of a paediatric patient with SLE who was later found to have developed AIH.

CASE PRESENTATION/INVESTIGATIONS/ DIFFERENTIAL DIAGNOSIS

A 15-year-old African-American girl with a medical history of SLE presented to the emergency room in July with a 7–10 day history of worsening abdominal pain and distention, vomiting, diarrhoea and fever. She also reported one episode of haemoptysis

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and increasing malaise. She had neither arthralgias, chest pain, respiratory distress nor rashes. Initial diagnosis of SLE 1 year prior per Systemic Lupus International Collaborating Clinics (SLICC) criteria included arthritis, characteristic rash, hypocomplementaemia, positive anti-double-stranded DNA and a strong family history of SLE. Liver function at the time of initial SLE diagnosis showed a mild transaminitis that was about three times the upper limit of normal. The patient had been on multiple medications previously, including hydroxychloroquine, methotrexate and methylprednisolone, but as of 4 months prior to this acute presentation, she had been off all immunosuppressive therapy and was taking only occasional naproxen. On physical examination, she was noted to have mild scleral icterus, abdominal distension with hepatomegaly palpable 4 cm below the costal margin and a palpable spleen tip. The examination

was negative for asterixis, fluid-wave shifts of the abdomen, Kayser-Fleischer rings and joint redness. Mental status examination was normal.

Initial laboratory studies included a complete blood count with differential, chemistries and liver function tests. Results are listed in [table 1](#), along with the remainder of the studies obtained throughout the hospital stay. The aetiology of the hepatitis was most concerning and numerous differentials, including infectious aetiologies, α -1-antitrypsin deficiency, Wilson's disease and drug toxicity, were considered. Specifically, in our patient, a normal alkaline phosphatase level suggested a hepatocellular rather than cholestatic pattern of transaminitis. Normal lipase argued against pancreatic origin. A normal iron and iron binding capacity ruled out haemochromatosis. Ammonia was mildly elevated with no clinical signs of hepatic

Table 1 Laboratory study results

Laboratory results		Comment
WCC	3.1 K/mm ³	Normal: 4–11
Haemoglobin; haematocrit	12.2 gm/dL; 36%	WNL
Platelets	212 K/mm ³	WNL
AST/ALT	3386/2891 units/L	Normal: <32
Total bilirubin	2.7 mg/dL	Normal: <1.2
ESR	36 mm/h	Normal: 0–20
BUN/creatinine	10/0.6 mg/dL	WNL
INR/PT	1.7/17.3 s	Elevated
Lipase	49 units/L	WNL
GGTP	110 units/L	Normal: 5–36
Alkaline phosphatase	153 units/L	WNL
CK	185 units/L	WNL
Albumin	4.1 gm/dL	WNL
TSH/free T4	0.76 mIU/mL; 0.95 ng/d	WNL
α -1-Antitrypsin	246 mg/dL	Normal: 90–200
Urinalysis	SG 1.011, 1+ ketones, 1+ HgB, 1 RBC	
Iron/total iron binding capacity	48/313 μ g/dL	WNL
% Iron saturation	15%	Normal: 20–55
Ammonia	35–55 μ mole/L	Normal: 11–51
Ceruloplasmin	34 mg/dL	WNL
24 h Urinary copper excretion	592 μ g	no reference <16 year
C3/C4	90/20 mg/dL	WNL
CH 50	47 units/mL	WNL
Acetaminophen level	<15 mg/L	
HepBsAb, HepBsAg, HepBcAb	Positive/negative/negative	
HepA IgM, HepC Ab, HepE IgM, HepE IgG	Negative	
HIV 1/2 Ab, HIV RNA PCR	Negative	
Mycoplasma pneumoniae IgM	<770 units/mL	WNL
EBV viral capsid IgG/IgM	510/<36 units/mL	Positive/negative
Ferritin	1418 ng/mL	Normal: 6–70
Triglycerides	157 mg/dL	Normal: 0–100
Fibrinogen	236 mg/dL	WNL
Total IgG	1351 mg/dL	Normal: 716–1711
Anti-liver–kidney antibody	<5.0	Normal: <20
Anti-smooth muscle antibody	Negative	
ANA	1:800 speckled/1:100 homogeneous	Positive
dsDNA	126 IU/mL	Normal: <30
Urine toxicology screen	Negative	
Respiratory pathogen PCR panel	Negative for 14 viruses and 3 bacteria tested	

Ab, antibody; ALT, alanine transaminase; ANA, antinuclear antibody; AST, aspartate transaminase; BUN, blood urea nitrogen; CH, Complement, total; CK, creatine kinase; dsDNA, double-stranded DNA; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; GGTP, gamma-glutamyl transpeptidase; HepA, Hepatitis A; HepBcAb, hepatitis B core antibody; HepBsAb, hepatitis B surface antibody; HepBsAg, hepatitis B surface antigen; HgB, hemoglobin; INR, international normalised ratio; PT, prothrombin time; RBC, red blood cell; SG, specific gravity; SBP, spontaneous bacterial peritonitis; TSH, thyroid-stimulating hormone; WCC, white cell count; WNL, within normal limits.

encephalopathy. Normal creatine kinase and complement levels argued against myositis and lupus flare. Macrophage activation syndrome (MAS)/haemophagocytic lymphohistiocytosis was considered as there have been associations with certain rheumatological conditions, but laboratory studies, as shown in table 1 (ferritin, triglycerides), did not support this.¹² Despite the low suspicion for MAS, natural killer cell function and soluble interleukin 2 receptor level were sent and returned negative several weeks later. Additional autoimmune aetiologies were tested for and ruled out. Abdominal ultrasound revealed increased echogenicity in the periportal regions, consistent with acute hepatitis and splenomegaly, as well as a small amount of ascites. Ultrasound showed evidence of neither biliary obstruction nor cholecystitis. Gastroenterology, rheumatology and infectious disease subspecialists were consulted. The patient had evolving liver failure as evidenced by the trend of her international normalised ratio (INR) and transaminases. She was treated symptomatically with metoclopramide for nausea and hydromorphone for pain control, because of their limited hepatic metabolism profiles. She continued to spike fevers during the first night of admission, so blood cultures were obtained and she was started on intravenous piperacillin/tazobactam due to concern for spontaneous bacterial peritonitis (SBP).

The following day, a liver biopsy with paracentesis was performed (figure 1). Ascitic fluid studies were not consistent with SBP. Liver biopsy demonstrated marked lobular and portal inflammation with the inflammatory infiltrate consisting of plasma cells, lymphocytes, histiocytes, neutrophils and occasional eosinophils. In addition, the biopsy demonstrated numerous apoptotic bodies, with evidence of neither steatosis, fibrosis nor necrosis. Pathology was consistent with severe acute hepatitis, favouring AIH.

TREATMENT/OUTCOME AND FOLLOW-UP

On the basis of 1999 IAHG revised criteria for the diagnosis of AIH, our patient scored 17, which placed her in the 'definite'

Figure 1 Liver biopsy histological picture. Liver biopsy (clockwise from top left): portal and lobular inflammation ($\times 20$). Portal inflammation and interface hepatitis ($\times 60$). Lobular inflammation with dying hepatocytes ($\times 40$). Trichrome stain demonstrating absence of fibrosis ($\times 10$).

AIH category prior to treatment.⁶ While our patient did not have elevated IgG or the complete histological characteristics on liver biopsy, she did have numerous other findings including severely elevated transaminases, positive ANA titres and findings of lymphoplasmacytic infiltrate on biopsy. In 2008, the IAHG diagnostic criteria were further simplified due to the complexity and original use for scientific purposes (as opposed to clinical). Using the simplified criteria, we would have not been able to diagnose even probable AIH.⁷ Owing to the variability in presentation of patients who are ultimately diagnosed with AIH, the simplified criteria may have oversimplified the scoring system, leading to less definitive diagnosis if the original scoring system is not applied. Owing to the high mortality in untreated AIH (5-year mortality $>50\%$) and no definitive clinical test for confirmation, it was decided to proceed with steroid treatment.⁷

The patient was started on intravenous methylprednisolone 1 mg/kg/day for 5 days, and responded within 48 h with resolution of clinical symptoms and improvement in serological liver markers as well as return of synthetic liver function. All other medications were stopped and the patient was discharged home on high-dose prednisone with a slow taper.

Two week follow-up in the gastroenterology office revealed non-adherence with steroid therapy and liver function tests that had risen since discharge. The patient was started on adjunctive azathioprine for its steroid sparing effect after checking the thiopurine methyltransferase activity level (to determine her processing ability of this medication). Six weeks after starting azathioprine, her liver enzymes had normalised. Follow-up 9 months later continued to show the patient was doing well.

DISCUSSION

The onset of AIH is usually chronic, which is why it used to be known as chronic active hepatitis when initially described. However, in 25% of cases, the presentation of AIH can be acute at onset.^{13 14} Typically, the diagnosis of AIH may consist of a constellation of findings, including abnormal liver function enzymes, elevated immunoglobulins, certain autoantibodies and characteristic histological findings on liver biopsy.²

While AIH can often be a part of many overlap syndromes of liver disease, including primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune sclerosing cholangitis and inflammatory bowel disease, there are comparatively fewer cases in the literature of patients with liver dysfunction having SLE and AIH.⁵

In our patient, biochemical liver function enzymes were found to be nearly 100 times the upper limit of normal. Severe hepatic dysfunction in combination with prolonged prothrombin time and hypoalbuminaemia is typically associated with patients with AIH who are ANA/SMA positive, although our patient was only ANA positive.¹⁵ Liver dysfunction tends to be mild in SLE. It is estimated that 25–50% of all patients with SLE have some degree of abnormal liver function tests at some point during their illness.¹⁶ It is the degree of abnormal liver functions that can sometimes make differentiating liver disease such as AIH and hepatic dysfunction as a part of SLE difficult. In concurrence with the severe presentation of our patient, AIH has been found to have a more acute presentation in children in comparison with middle-aged adults.¹⁵ It has been suggested to use anti-ribosomal P protein antibody as a marker of SLE hepatitis as opposed to AIH, however, evidence is controversial as some patients with AIH alone have also been positive.¹⁷ Histological evidence is typically necessary to differentiate between AIH and SLE.^{16–18}

Little is known about liver disease in paediatric patients with SLE as compared with adult patients with SLE. In one British study by Irving *et al*,¹⁹ it was found that the prevalence of AIH in the juvenile SLE population was 9.8% (9 of 92 patients) in comparison with 1.3% of adults (5 of 377 patients).²⁰ Interestingly, all of the paediatric patients in that study developed AIH prior to developing SLE, but in our patient, she had a diagnosis of SLE approximately 1 year prior to her current diagnosis of AIH.¹⁸ Runyon *et al*²¹ found 43 of the 206 patients with SLE had biochemically evident liver function abnormalities and, of those, 4 had biopsy-proven AIH, which is also referred to as chronic active hepatitis. In the population of this study, 28% were diagnosed with liver disease >1 year post-SLE diagnosis while 45% were diagnosed with liver disease as well as SLE within the same year.²¹ A Japanese study by Takahashi *et al*¹⁷ showed liver dysfunction in 123 of the 206 patients with SLE, of which 6 (4.9%) were histologically confirmed to have AIH. Chowdary *et al*²² reported 6 of the 40 patients with SLE were also diagnosed with AIH. There is a case report of a 12-year-old girl from Turkey who developed an overlap syndrome involving AIH and SLE.¹¹ Another case report from Egypt identified a 12-year-old girl who initially presented with AIH and 4 years later developed SLE.²⁰ Aside from Irving *et al*'s study, the literature mostly contains data on adults. The literature does contain occasional case reports describing paediatric patients with SLE as well as AIH, but there is no concise review or cohort study.

In conclusion, our patient was shown to have significant improvement of her biochemical liver function tests soon after starting steroids. Despite not meeting definitive 2008 criteria for AIH, our patient had pathology and laboratory studies highly suggestive of the diagnosis, and demonstrated a favourable response to AIH treatment. It is known that complete resolution of aminotransferases and synthetic function can take months, and relapse rates are high if treatment is stopped before 2 years.¹ Prognosis for our patient is difficult to determine at this point due to the severity of presentation at diagnosis in combination with the limited availability of data in the literature. It is evident that patients with liver dysfunction in SLE need a full evaluation for other causes of liver disease. It would be of benefit to conduct a multicentre case review to establish epidemiological as well as prevalence data of both AIH and SLE

in the same patient in the paediatric population. It would be interesting to see the level of liver dysfunction that may occur in AIH, as no clear parameters seem to have yet been established.

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Learning points

- ▶ Acute hepatitis in children has a broad differential including, but not limited to, infectious, drug-induced, rheumatological or genetic disorder.
- ▶ Autoimmune hepatitis is not a component of systemic lupus erythematosus.
- ▶ Autoimmune hepatitis is a diagnosis of exclusion that must fulfil specific diagnostic criteria.

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