Autoimmune haemolytic anaemia is a rare association with primary biliary cirrhosis

Introduction

Primary biliary cirrhosis is a progressive cholestatic liver disease. The aetiology is presumed to be autoimmune. Autoimmune haemolytic anaemia is either idiopathic or secondary to autoimmune conditions, haematological malignancies or medications. Appropriate investigation can expedite diagnosis in patients with abnormal baseline liver function.

Discussion

Primary biliary cirrhosis is an autoimmune condition occurring most commonly in middle-aged females. It causes non-suppurative granulomatous inflammation mainly affecting the interlobular bile ducts. This progresses to fibrosis causing cholestasis, cirrhosis and portal hypertension. Around 80% of patients with primary biliary cirrhosis have a second autoimmune condition (Nakasone et al, 2000; Medeiros and Setubal, 2004). Autoimmune haemolytic anaemia is idiopathic in 50% of cases and is more usually associated with underlying lymphoproliferative or autoimmune disease (Fuller et al, 2003; Medeiros and Setubal, 2004).

The combination of primary biliary cirrhosis and autoimmune haemolytic anaemia presents a diagnostic difficulty in that rising serum bilirubin levels could be assumed to be a worsening of the primary biliary cirrhosis. Haemolysis occurs in 50% of patients with cirrhosis, independent of the cause, and this is not clearly understood (Brackstone and Ghent, 2000). Various mechanisms have been suggested including bile causing immune dysregulation (as chenodeoxycholic acid acts as an immunosuppressant in vitro) and directly causing red blood cell membrane dysfunction. The latter could subsequently lead to antigen exposure and formation of new autoantibodies against red blood cells. These mechanisms may not only explain the reasons for ursodeoxycholic acid alone resulting in clinical resolution (as with a mild case of haemolysis) (Fuller et al, 2003), but also the fact that none of the previously described cases have had autoimmune haemolytic anaemia preceding their diagnosis of primary biliary cirrhosis. Some have presented with

Table 1. Comparison of blood results on baseline, day 1 and day 3 admission, 3 weeks post admission, at relapse and currently (remission)

Investigation	Baseline	D1	D3	D21	Relapse	Remission
Bilirubin (umol/litre)	15	48	56	13	31	8
Alkaline phosphatase (u/litre)	161	347	341	74	82	75
Alanine transaminase (u/litre)	21	69	85	19	13	13
Gamma-glutamyl transpeptidase (u/litre)	30	363	355	133	53	78
Haemoglobin (g/dl)	9.5	7.4	10.4	12.8	8.5	139
Mean cell volume (fl)	99.4	113.7	101	106	103.3	87.2
Platelets (10^9/litre)	357	352	334	300	235	214
Lactate dehydrogenase (iu/litre)	-	-	695			
Reticulocytes (10^9/litre)	-	-	215		222.1	32.2

CASE REPORT

A 42-year-old woman presented with a 3–4-week history of pallor, lethargy, shortness of breath, weight loss and obstructive jaundice. She had a 4-year history of primary biliary cirrhosis, was not on any medications and had a family history of autoimmune thyroid disease.

On examination she was stable with mild jaundice and hepatosplenomegaly. Her blood results are shown in *Table 1*.

Initial investigations revealed normal haematinics, haemoglobin, electrophoresis and gastroscopy. Ultrasound confirmed hepatosplenomegaly with no biliary duct dilation and multiple small gallstones. She was started on ursodeoxycholic acid as it was thought this was a decompensation of her primary biliary cirrhosis.

On the third day of admission (post transfusion) her serum bilirubin level was rising. A high reticulocyte count and lactate dehydrogenase, positive direct Coombs' test, blood film revealing rouleaux and spherocytes, and a bone marrow aspirate showing hypercellular bone marrow with erythroid hyperplasia all pointed to autoimmune haemolysis.

She was started on prednisolone 60 mg daily. Symptomatically and biochemically she was steroid responsive. Interval blood tests showed an improvement and her prednisolone was weaned over 3 months. She relapsed 2 years later and was restarted on prednisolone 60 mg daily and azathioprine was added. The prednisolone was weaned and she remains stable on azathioprine 50 mg daily.

Dr S Meade is Core Medical Trainee in the Department of Gastroenterology, Queen Elizabeth Hospital, London SE18 4QH

Dr S Kotha is Gastroenterology Registrar in the Department of Gastroenterology, Queen Elizabeth Hospital, London

Dr A Gera is Gastroenterology Consultant in the Department of Gastroenterology, Queen Elizabeth Hospital, London

Dr A Loganayagam is Gastroenterology Consultant in the Department of Gastroenterology, Queen Elizabeth Hospital, London

Correspondence to: Dr S Meade (smeade@doctors.org.uk)

concurrent symptoms although primary biliary cirrhosis is often diagnosed after an asymptomatic period (Tian et al, 2009). This would suggest that the link between the two conditions might be associated with the natural history of disease progression in primary biliary cirrhosis as well as the underlying autoimmune predisposition. The significance of the latter is highlighted by cases of autoimmune haemolytic anaemia in patients with primary biliary cirrhosis a number of years after liver transplant (Retana et al, 2007). Some cases have been successfully treated with ursodeoxycholic acid alone (Fuller et al, 2003; Gentile et al, 2009). The current case is an example of where ursodeoxycholic acid alone has failed and high-dose immunosuppression was required.

This case adds to the small number of reported cases. It is important to evaluate the rising bilirubin level in conjunction with other biochemical markers. Anaemia in patients with chronic liver disease often leads to endoscopy as first-line investigation to rule gastrointestinal bleeding. However, a significant rise in bilirubin levels out of proportion to the rise in alkaline phosphatase levels, anaemia with no active bleeding and a macrocytosis with a high reticulocyte count and lactate dehydrogenase can help expedite the diagnosis in these patients. **BJHM**

LEARNING POINTS

- Autoimmune liver disease is associated with other autoimmune phenomena, including haemolysis.
- Significant anaemia and rising bilirubin levels out of proportion to a rise in alkaline phosphatase levels should prompt investigation for haemolysis to expedite diagnosis.

Brackstone M, Ghent CN (2000) Primary biliary cirrhosis and hemolytic anemia confusing serum bilirubin levels. *Can J Gastroenterol* **14**: 445–7

Fuller SJ, Kumar P, Weltman M, Wiley JS (2003) Autoimmune hemolysis associated with primary biliary cirrhosis responding to ursodeoxycholic acid as sole treatment. *Am J Hematol* **72**: 31–3 (doi: 10.1002/ajh.10252)

Gentile M, Verta M, Vigna E et al (2009) Autoimmune hemolytic anaemia concomitant with sequential autoimmune hepatitis-primary biliary cirrhosis overlap syndrome and hashimoto's thyroiditis: a new entity of autoimmune polyendocrine syndrome. *J Endocrinol Invest* **32**: 287–8 (doi: 10.1007/BF03346469)

Medeiros CRD, Setubal DC (2004) Autoimmune hemolytic anemia as a complication of primary biliary cirrhosis. *Hematology and Bone Marrow Transplantation Service* **21**: 153

Nakasone H, Sakugawa H, Fukuchi J et al (2000) A patient with primary biliary cirrhosis associated with autoimmune hemolytic anemia. *J Gastroenterol* **35**: 245–9

Retana A, Kaplan M, Erban J (2007) Autoimmune haemolytic anemia in patients with liver transplants for primary biliary cirrhosis: Three case reports and review of the literature. *Am J Gastroenterol* **102**: 197–200 (doi: 10.1111/j.1572-0241.2006.00810.x)

Tian Y, Wang C, Liu J-X, Wang H-H (2009) Primary biliary cirrhosis-related autoimmune hemolytic anemia: three case reports and review of the literature. *Case Rep Gastroenterol* **3**: 240–7 (doi: 10.1159/000229189)

Skin lesions in calciphylaxis

A 68-year-old woman with end-stage renal failure on haemodialysis underwent revascularization of the foot. A few days after admission, she developed painful necrotic skin lesions on the breast (*Figure 1*), abdomen and arms (*Figure 2*). The patient had been treated with high dose vitamin D for hypocalcaemia on admission, resulting in a rapid shift in serum calcium. The diagnosis of calciphylaxis was established clinically and incisional skin biopsy was non-specific.

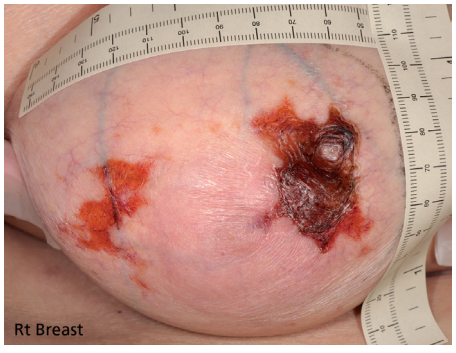
Dr Lisa C Kirby is Specialty Doctor in Dermatology in the Department of Dermatology, Ormskirk District General Hospital, Ormskirk L39 2AZ

Dr Khaled Abdulnabi is Consultant Nephrologist in the Department of Nephrology, Wirral University Teaching Hospital, Wirral

Correspondence to: Dr LC Kirby (lisaclairekirby@gmail.com)

The painful skin lesions developed suddenly and progressed rapidly, starting as purple discolouration (retiform purpura). Lesions generally develop on the lower extremities in areas of adiposity, but may occur in any area (Nigwekar et al, 2015). Ulcerated lesions typically form black eschar and secondary infection may occur; ulceration increases the associated mortality to 80% (Weenig et al, 2007).

Figure 1. Right breast.



This patient was treated with analgesia, wound care, sodium thiosulphate and daily dialysis. She unfortunately deteriorated and died 6 weeks after the presentation of the skin lesions. **BJHM**

Nigwekar SU, Kroshinsky D, Nazarian RM et al (2015) Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis* **66**(1): 133–46 (doi: 10.1053/j.ajkd.2015.01.034)

Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR (2007) Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* **56**(4): 569–79 (doi: 10.1016/j.jaad.2006.08.065)

Figure 2. Right arm.