Submitted February 2020; Accepted July 2020

CASE REPORT

Jaundice due to autoimmune haemolytic anaemia in a patient with Gram-negative septic shock

M.A. Lantinga[1,2], F.N. Polderman[1], D.E. Issa[3], C.P.C. de Jager[1]

Departments of [1]Intensive Care, [2]Gastroenterology and Hepatology and [3]Haematology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands

Correspondence

M.A. Lantinga - martenlantinga@gmail.com

Keywords - **jaundice, E. coli, autoimmune haemolytic anaemia, AIHA**

Abstract

Toxic shock syndrome and sepsis-induced cholestasis are the foremost common causes of jaundice in the intensive care unit. A rare cause of jaundice is autoimmune haemolytic anaemia (AIHA). We present a case in which recurrent *Escherichia coli* sepsis induced a Coombs-positive AIHA leading to jaundice. Although AIHA induced by Gram-negative shock is rare, it needs to be considered in the absence of alternative causes to prevent delay of treatment.

Introduction

Jaundice in the intensive care unit (ICU) has a broad differential diagnosis, with toxic shock syndrome (i.e. hepatic hypoxia) and sepsis-induced cholestasis, predominantly linked to infections with Gram-negative bacteria, being the foremost common causes.[1, 2] Using the SOFA score, sepsis-induced liver dysfunction is quantified by measuring serum total bilirubin, with levels ≥20 µmol/l indicating some degree of hepatic involvement.[3] Sepsis-induced liver dysfunction is frequent and associated with increased mortality, although it is uncertain if elevated serum bilirubin during sepsis truly reflects a pathological condition or is just a mere reflection of altered bile production and transport into the systemic circulation.[4] A rare cause of jaundice is autoimmune haemolytic anaemia (AIHA).[5] In Coombs-positive AIHA, antibodies directed against red blood cells are produced, leading to haemolysis. Coombs-positive AIHA has a broad differential diagnosis, with viral and mycoplasmal infections being the leading cause of secondary AIHA.[6] We present a patient who was admitted to the ICU in whom Escherichia coli septic shock induced hyperbilirubinaemia as a result of AIHA.

Case Report

A 71-year-old man, with a history of ischaemic cerebrovascular disease, unexplained anaemia, choledocholithiasis, cholecystectomy, urolithiasis and recurrent orchiditis with recent use of fluoroquinolones (ciprofloxacin and levofloxacin) for epididymitis, presented to the emergency department (ED) with severe abdominal pain and discoloured urine. Physical examination showed jaundice, elevated respiratory rate (22 breaths/min), hypotension (84/52 mmHg) and tachycardia (100 beats/min) in the absence of fever or altered mentation. Abdominal examination revealed painful percussion, tenderness and guarding. Scrotal examination showed status after unilateral orchidectomy and no sign of orchiditis or epididymitis. Laboratory investigations revealed anaemia (haemoglobin 6.7 mmol/l, N: 8.5-11.0) with sign of haemolysis (haptoglobin <0.08 g/l, N: 0.40-2.40; reticulocytes 154 x10^9/l, N: 25-120), severe leukocytosis (53.7 x 10^9/l, N: 4.0-10.0, differential: >95% neutrophils, no fragmentocytes), prolonged prothrombin time (38 sec, N: 12-15) and prolonged activated partial thromboplastin time (64 sec, N: 26-36) with only mildly impaired antithrombin (65%, N: 80-120). Blood platelets were normal (249 x 10^9/l, N: 150-400) whereas lactate dehydrogenase could not be determined due to haemolysis. Renal function was impaired (eGFR CKD-epi 29 ml/min/1.73 m^2, N: >90) with severe hyperbilirubinaemia (unconjugated bilirubin 408 µmol/l, N: 0-16), low albumin (28 g/l, N: 35-50), mildly elevated liver enzymes (ALT 137 U/l, N: 0-44; gamma-glutamyltransferase 104 U/l, N: 0-54), raised inflammatory markers (C-reactive protein 80 mg/l, N: 0-8; procalcitonin >75 ng/ml, N: 0-0.5) with normal serum glucose (4.5 mmol/l, N: 4.0-7.7) and ammonia levels (32 µmol/l, N: 10-35). In the ED, we performed abdominal radiography and ultrasonography, both of which were unremarkable, excluding urolithiasis, and single doses of cefuroxime, metronidazole and tobramycin were given.

He was admitted to our ICU under the diagnosis of severe septic shock with multiorgan failure combined with disseminated intravascular coagulation and haemolysis without evident

Table 1. Differential diagnosis of jaundice at the intensive care unit

Prehepatic	Intrahepatic	Extrahepatic
Haemolysis	Sepsis	Pancreatitis
Heart failure	Ischaemia/hypoperfusion state	Biliary tract stricture
Advanced cirrhosis	Drug-induced liver injury (e.g. acetaminophen)	Biliary tract obstruction
	Total parenteral nutrition	
	Postoperative cholestasis	
	Viral hepatitis (A, B, C (+D), E)	
	Non-viral hepatitis (alcoholic, non-alcoholic)	
	End-stage liver disease	
	Non-hepatitis infections (e.g. HIV; CMV; EBV)	
	Haemophagocytic syndrome	

CMV = cytomegalovirus; EBV = Epstein-Barr virus.

cause (Apache II score 31; Apache IV score 103; SOFA score 15). Computed tomography of the thorax and abdomen were unremarkable, except for minimal unilateral perinephric stranding. Antibiotics were switched to meropenem because of previous culture results showing drug-resistant *Escherichia coli*. High-dose steroids (prednisolone 60 mg daily), combined with folic acid and supplementation of calcium and vitamin D, were initiated under the suspicion of secondary autoimmune haemolytic anaemia because the direct antiglobulin test (i.e. direct Coombs test) was strongly positive for complement, weakly positive for IgG and IgM and showed a borderline presence of cryoglobulins (typing performed when haemolysis was reduced under prednisolone). We started continuous venovenous haemodialysis because of renal failure. Both urine and blood cultures returned positive for *E. coli*. Meropenem was switched to cefuroxime based on sensitivity results. To further investigate hyperbilirubinaemia *(table 1)*, additional tests were performed. Serological testing was negative for other autoimmune diseases (tested: antinuclear antibodies, anti-mitochondrial antibodies, anti-neutrophilic cytoplasmic autoantibodies) and active viral infection (tested: parvovirus; viral hepatitis A, B, C and E; HIV; cytomegalovirus; Epstein-Barr virus; varicella-zoster virus and herpes simplex virus). Leptospirosis and capnocytophaga canimorsus infection were not suspected. To exclude lymphoma and alternative infection sources, ^{18}fluorodeoxyglucose positron-emission computed tomography (^{18}F-FDG PET/CT) was performed, which showed no relevant findings. Magnetic resonance cholangiopancreatography showed an unremarkable biliary system, specifically no biliary tract obstruction or stricture. Bone marrow biopsy after one week and one month showed a reactive state and no signs of haemophagocytic syndrome or lymphoma.

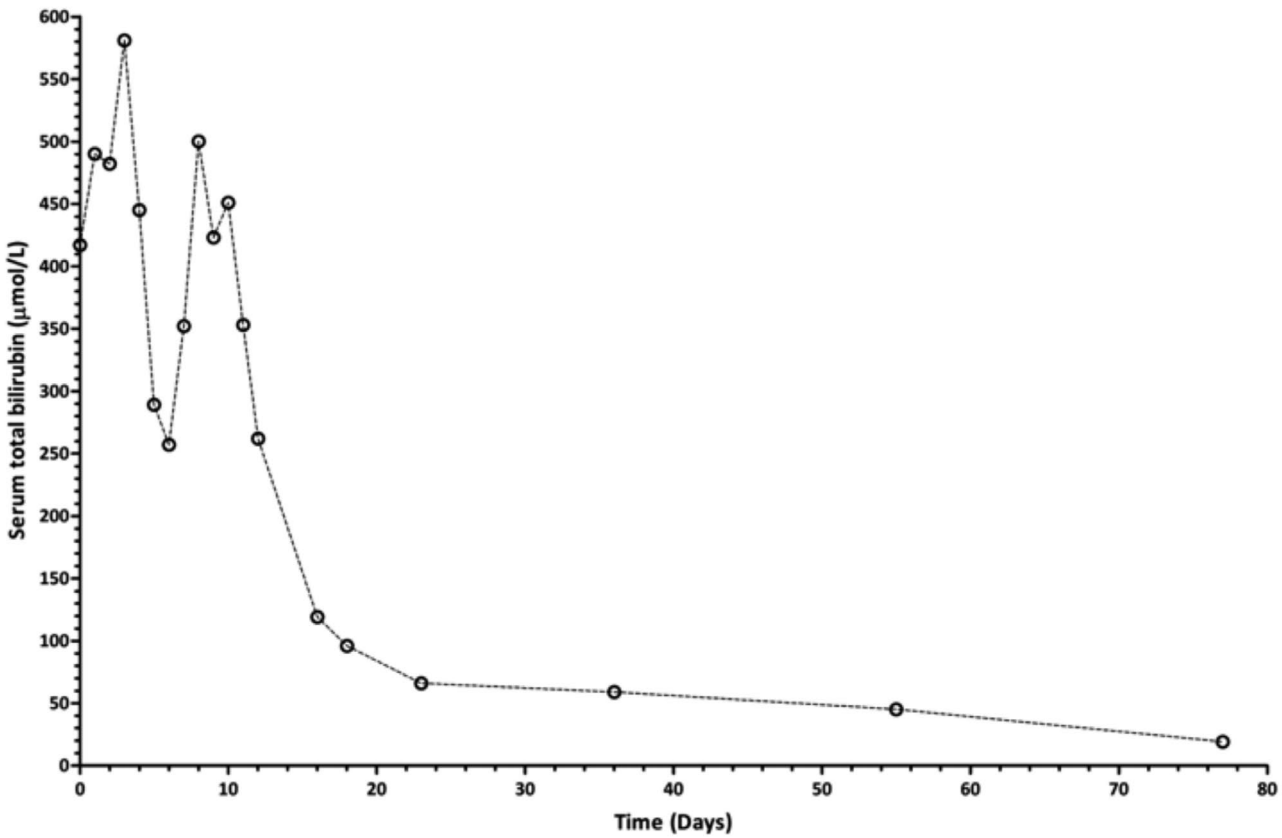

Figure 1. Course of serum total bilirubin over time

Eventually bilirubin levels decreased after reaching a peak value of 581 µmol/l *(figure 1)*. Corticosteroid treatment was tapered and antibiotic treatment was stopped after the patient stabilised. Following antibiotic treatment the direct Coombs test remained strongly positive for complement (C3d) and positive for IgM. He was discharged to the nephrology medical ward for further recovery. After discharge, renal function recovered and ultimately outpatient intermittent haemodialysis could be stopped.

Discussion

We present a patient with Gram-negative septic shock induced Coombs-positive AIHA which led to severe jaundice.

In retrospect, the combination of the patient's medical history, abdominal pain, perinephric stranding and *E. coli* in both urine and blood cultures, without other evident explanation, could lead to the working diagnosis of *E. coli* urosepsis. However, as there was a discrepancy between the level of hyperbilirubinaemia and severity of sepsis, other potential causes of hyperbilirubinaemia were investigated. Although *E. coli* sepsis is common, having AIHI due to *E. coli* is rare, suggesting a specific susceptibility in our patient for pathogen specific factors. Cold agglutinin disease was considered, but this diagnosis was considered unlikely because of a good response to prednisolone therapy and absence of typical symptoms in our patient. Ultimately, the diagnosis of *E. coli* sepsis induced AIHA was deemed the most likely cause for the high bilirubin level at presentation.

A review of the literature revealed only one reference to *E. coli* induced Coombs-positive AIHA.[6] As stated earlier, mycoplasmal and viral infections are typically seen as infectious aetiology, with a peak incidence seen at the age of 70 years. Infectious causes lead to a transient form of AIHA, in contrast to lymphoproliferative disorders. Onset of symptoms of AIHA is in line with the response of the body's immune system and is seen in week two and three after infection. In severe cases AIHA can lead to haemoglobinuria and transient renal failure, as was seen in our patient. Treatment of this transient cause of AIHA consists of supportive care in the form of intensive hydration, limited blood transfusion (as this can induce additional haemolysis) and prednisone treatment to maintain adequate renal blood flow.[6]

In conclusion, we present a unique case of a patient presenting with Coombs-positive AIHA induced by an *E.coli* sepsis. However rare, AIHA must be considered in patients presenting with sepsis and signs of haemolysis without evident cause, so that adequate treatment can be timely initiated.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received. Informed consent was obtained from the patient for publication of this case report.

References

1. Nesseler, N., et al., Clinical review: The liver in sepsis. Crit Care, 2012. 16(5): p. 235.
2. Trauner, M., P. Fickert, and R.E. Stauber, Inflammation-induced cholestasis. J Gastroenterol Hepatol, 1999. 14(10): p. 946-59.
3. Vincent, J.L., et al., The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med, 1996. 22(7): p. 707-10.
4. Jenniskens, M., et al., Cholestatic liver (dys)function during sepsis and other critical illnesses. Intensive Care Med, 2016. 42(1): p. 16-27.
5. Michel, M., Classification and therapeutic approaches in autoimmune hemolytic anemia: an update. Expert Rev Hematol, 2011. 4(6): p. 607-18.
6. Gehrs, B.C. and R.C. Friedberg, Autoimmune hemolytic anemia. Am J Hematol, 2002. 69(4): p. 258-71.