The erroneous perception of a clinical sign: Cholestasis preceding sepsis mimicking hepatitis in an adolescent patient

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ABSTRACT

Background: In children and adolescents, isolated cholestasis rarely is a first clinical sign of severe sepsis.

Case: A previously healthy 14-year-old adolescent had severe *S. aureus* sepsis. Delayed diagnosis required a prolonged antimicrobial treatment.

Conclusion: This unique case illustrates the importance of considering jaundice as an early sign of sepsis.

ABBREVIATIONS

BP – blood pressure

CRP – C-reactive protein

CT – computed tomography

FBC - full blood count

IBI – invasive bacterial infection

IVAB – intravenous antibiotic

MRI – magnetic resonance imaging

PED- pediatric emergency department

PICU - pediatric intensive care unit

SBI - severe bacterial infection

US – Ultrasound study

KEY CLINICAL MESSAGE

Jaundice should be considered as a first clinical sign preceding severe invasive bacterial infection or sepsis in patients of all ages including childhood and adolescence. Early laboratory investigations and MR imaging studies for osteomyelitis or myositis are paramount to avoid progression to life-threatening sepsis and significant morbidity and mortality.

INTRODUCTION

Jaundice and cholestasis are frequently present in sepsis.[1] In contrast cholestasis has rarely been reported as an isolated first manifestation of invasive bacterial infection (IBI) or sepsis in childhood and adolescence. Thus, diagnosis of sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection may be delayed and cause significantly increased morbidity.[2] With a renewed focus on organ dysfunction in the Third International Consensus Definitions for Sepsis and Septic shock (Sepsis-3) (2016) in adults, cholestasis should be considered as one of the key clues to sepsis in all ages.[2] Clinically, organ dysfunction is most commonly depicted by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of ≥ 2 points which in turn is associated with an in-hospital mortality greater than 10%.[3]

CASE REPORT

We report a case of prolonged jaundice without fever presenting itself as sepsis due to multifocal *S. aureus* osteomyelitis. A previously healthy 14-year-old adolescent male presented to our pediatric emergency department (PED) with a 5-day history of left ankle pain and jaundice without fever. Two days before, left ankle X-rays and computed tomography

(CT) imaging had been normal. He reported a camping holiday in Italy not long ago, but no trauma, animal contact, drug abuse or sexual activity. Clinical examination showed a patient in good general condition with normal vital signs but markedly jaundiced. He described stabbing pain in his left ankle without signs of swelling, warmth or erythema. Laboratory variables included raised total bilirubin (103umol/L; liver SOFA score 3), low platelets (84G/L; coagulation SOFA score 2), raised liver function tests (LFT) (ALAT 178U/L, ASAT 129U/L) and C-reactive protein (CRP) (195mg/L).[3] A full blood count (FBC) and coagulation tests were normal. The same day an abdominal ultrasound study (US) performed externally had shown hepatosplenomegaly without biliary duct obstruction. The patient was discharged home with a preliminary diagnosis of viral hepatitis but returned to our PED five days later. On physical examination, he was in poor general condition and tachycardic (220bpm), however, afebrile and normotensive. He was still markedly jaundiced and had increased left ankle tenderness, swelling and erythema. Newly added findings were bilateral wrist and dorsal forearm tenderness, swelling and erythema, generalized allodynia to tactile stimuli and pain-related inability to walk were noted. A diffuse palpable non-blanching purpuric rash (Fig. 1) was observed on the dorsal and ventral aspects of both legs and, to a lesser extent, on the face and volar side of the left forearm. Repeat laboratory testing showed a systemic inflammatory response syndrome (SIRS) with highly elevated inflammatory markers (CRP 223mg/L, leucocytes 29.7G/L) as well as more pronounced thrombocytopenia (53G/L; coagulation SOFA score 2) and hyperbilirubinemia (total bilirubin 328umol/L; SOFA score 4), acute kidney failure (creatinine 166umol/L; SOFA score 1) and further raised LFTs (ASAT 268U/L, ALAT 189U/L, GGT 168U/L).[3] The patient was admitted to the pediatric intensive care unit (PICU) with a preliminary diagnosis of systemic vasculitis versus bacterial sepsis and started on empiric intravenous broad-spectrum antibiotic (IVAB) therapy. Blood cultures grew Methicillin-sensitive *Staphylococcus aureus.* Total-body magnetic resonance imaging (MRI) confirmed extensive osteomyelitis of the left ankle and calcaneus, right femur,

and second right rib, myositis and fasciitis of the right forearm, right upper and left lower leg and multiple septic embolisms in the lungs (Fig. 2). Despite an intensified IVAB regimen with floxacillin and clindamycin, the patient remained bacteremic until day seven of hospital admission. Echocardiography ruled out endocarditis and there was no serological evidence of viral hepatitis, leptospirosis, rickettsiosis, or an autoimmune process. Due to the severe course of the disease an immunological work-up was performed but no evidence of underlying immune deficiency, in particular, chronic granulomatous disease was found. The bacteremia only resolved once the bone abscess in his left calcaneus was surgically drained on day seven. Poor wound healing required repeated surgical interventions on day 12 and 19 and the patient was finally discharged home after 30 days.

DISCUSSION

Isolated cholestasis preceding sepsis has been previously reported in adult patients but only scarcely in children and adolescents.[4,5] Whereas in the absence of fever and abnormal vital signs physicians may be more inclined to consider viral hepatitis, inherited disorders or autoimmune diseases as possible causes of cholestasis, the high liver (SOFA 2) and coagulation (SOFA 2) SOFA scores already at initial presentation and the further increased liver SOFA score on representation (SOFA 4) should have facilitated early recognition of a patient with sepsis or at risk for sepsis (SOFA).[3]

Hepatic injury is a well described complication of late sepsis and accounts for up to 20% of cholestatic jaundice in patients of all ages.[1] In our current understanding of the pathophysiological processes involved, pro-inflammatory cytokines cause downregulation of hepatocellular transport systems, bile formation and flow, resulting in hepatocellular and ductular cholestasis without biliary obstruction.[1,6] In children, this phenomenon is mostly seen in newborns and infants with urinary tract infections.[7] Likewise, we did not initially consider

jaundice as an early sign of sepsis and diagnosis and initiation of IVAB were delayed by seven days which may have contributed to the severe disease course. In view of our patient's travel history and good general condition, the first line differential was symptomatic hepatitis A infection. Second-line differential diagnoses included infectious mononucleosis with hepatitis and extravascular hemolysis due to hypersplenism. Abdominal US ruled out mechanical obstruction of the bile ducts from choledochal cysts, cholelithiasis or compression from intra- and extrahepatic tumors.[8]Drug-in duced hepatocellular injury following the intake of analgesics was excluded. The simultaneous appearance of jaundice and ankle tenderness without local inflammatory signs or radiologic abnormalities in our case was initially misleading. In retrospect, considering the low sensitivity of X-ray and CT for the detection of early osteomyelitis, severe ankle pain without preceding trauma combined with the high inflammatory markers should have prompted MRI earlier.[9]

CONCLUSION

This case illustrates how putting into use of the updated Third International Consensus Definitions for Sepsis and Septic shock (Sepsis-3) will facilitate earlier recognition of cholestasis as a clinical sign of organ failure and more timely management of patients with sepsis or at risk of developing sepsis of all ages in the future.[2]

FIGURE LEGENDS

Figure 1. Generalized jaundice and a) Bilateral swelling and erythema of wrists and forearms b) Left ankle swelling and erythema and c) Diffuse palpable non-blanching purpuric rash on left ankle and dorsal and ventral aspects of both legs. *With permission of the patient and his parents.*

Figure 2. Total-body MRI on T2 turbo inversion recovery magnitude (TIRM) fat suppression (FS) sequences. a) Left distal femoral metaphysis osteomyelitis (orange arrow) and multifocal bilateral myositis of the lower extremities (white arrows). b) Maximum intension projection (MIP) reconstruction of multiple pulmonary septic embolisms (white arrows). c) Left ankle and calcaneus osteomyelitis (orange arrow).

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