CASE REPORT

Penicillin-induced liver injury during treatment for ocular neurosyphilis

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SUMMARY

A 51-year-old man, homosexual, recently diagnosed with ocular neurosyphilis, presented to the emergency room with a 1-day history of fevers and chills. His vital signs were significant for a temperature of 102.8°F and tachycardia of 125 bpm. The patient had experienced blurred vision in his left eye and was diagnosed with ocular neurosyphilis 10 days prior to the current presentation. He was treated with a 14-day course of high-dose intravenous penicillin and oral prednisone. His laboratory studies were significant for transaminitis, with an aspartate aminotransferase of 1826 U/L, alanine aminotransferase of 1743 U/L, total bilirubin of 1.2 mg/dL and alkaline phosphatase of 68 U/L. After ruling out viral aetiologies and toxin-induced hepatic injury, penicillin was discontinued on the day following admission and transaminases promptly improved with resolution of symptoms. The patient's vision returned to normal within 2 weeks after discharge from hospital.

BACKGROUND

Acute liver failure is defined as a rapid loss of hepatocyte function, with hallmark features of encephalopathy (any degree of altered mentation) and coagulopathy (International Normalised Ratio, INR ≥ 1.5).¹ The incidence of acute liver failure comprises of 2000 patients annually in the USA and accounts for 7% of liver transplants annually.¹ The US Acute Liver Failure Study Group found that acetaminophen accounts for nearly 50% of cases of acute liver failure, followed by drug-induced liver injury (12%), unclear aetiology (15%) and viral hepatitis (including hepatitis A or B) in 9% of cases.¹ While acetaminophen-induced liver injury results in median alanine aminotransferase (ALT) in the 3800 U/L range and only slightly elevated bilirubin, non-acetaminophen drug-induced liver injury results in lower ALT (median 685 U/L) levels and higher bilirubin levels (median 19.8 mg/dL).¹ Viral hepatitis causes elevated transaminases in the 1700–2100 U/L range with median bilirubin levels of 13–19 mg/dL.¹ Antibiotics are the leading cause of non-acetaminophen drug-induced liver injury, followed by non-steroidal anti-inflammatory drugs and anticonvulsants.^{1 2} The most frequently implicated antibiotic is amoxicillin-clavulanate, estimated to cause 1 case of jaundice in every 78 000 prescriptions.² Flucloxacillin, isoniazid and rifampin also dominate the list of hepatotoxic antibiotics in the WHO Safety Database.² Penicillin is more commonly associated with hypersensitivity reactions and has only rarely been associated with hepatic injury, as evidenced by the very few case reports

over the past several decades.² We describe a case of a patient with penicillin-induced liver injury during the course of treatment for ocular neurosyphilis.

CASE PRESENTATION

A 51-year-old man, homosexual, who had recently been diagnosed with left eye ocular neurosyphilis, presented to the emergency room with a 1-day history of fevers and chills. His vital signs were significant for a temperature of 102.8°F and tachycardia of 125 bpm. Ten days prior to presentation, the patient had been seen at an outside hospital, where he was diagnosed with neurosyphilis and uveitis with left retinal and optic nerve involvement via a lumbar puncture with positive rapid plasma reagin (RPR) titres. The patient was prescribed oral prednisone 60 mg daily and a 2-week course of high-dose intravenous penicillin (on day 10 of penicillin treatment on presentation). The dosage and type of penicillin used was aqueous crystalline penicillin G 24-million units per day as a continuous infusion administered via a peripherally inserted central catheter. On further questioning, he confirmed night sweats, chills and malaise but denied cough, chest pain, abdominal pain, diarrhoea and urinary symptoms. He denied any recent travel, sick contacts or intravenous drug use. He also denied recent acetaminophen use. He was sexually active with men, performing both oral and anal sex. He had had routine laboratory tests (including liver function tests) 3 months prior to presentation, which were all within normal limits. The patient's medical history was significant for hypertension and hyperlipidaemia, which were managed with diet and exercise. Of note, the patient was a non-smoker and had a 12-unit/week-alcohol history.

His physical examination was benign; the patient had no evidence of jaundice, scleral icterus, lymphadenopathy or stigmata of liver disease. His abdomen was non-tender and revealed neither hepatomegaly nor splenomegaly, and auscultation demonstrated normal bowel sounds. Laboratory investigation demonstrated normal serum albumin but significant transaminitis, with aspartate aminotransferase (AST) of 1826 U/L, ALT of 1743 U/L, total bilirubin of 1.2 mg/dL and alkaline phosphatase (ALP) of 68 U/L. Complete blood count was significant for normal haemoglobin of 13.3 g/L, white cell count (WCC) of $7.7 \times 10^9/L$ with 19% bandemia, thrombocytopenia of $110 \times 10^9/L$ and serum lactate level of 2.1 mmol/L. Coagulation profile revealed prothrombin time of 14.4 s and INR of 1.2. Chest X-ray showed no evidence of

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acute pulmonary abnormalities and urinalysis was normal. Work up for acetaminophen and salicylic acid levels was negative. Ultrasound of the abdomen to rule out Budd-Chiari syndrome showed normal hepatic and portal veins. The patient was initially treated empirically with vancomycin 1.25 mg twice daily and cefepime 2 g twice daily in case of sepsis, although these were discontinued following negative blood cultures.

The day following admission, the patient's AST increased to 2727 U/L, ALT to 3213 U/L and total bilirubin to 2.3 mg/dL. Gastroenterology and infectious disease specialists were consulted, who advised a full viral and autoimmune work up. The patient had negative antinuclear antibodies, negative hepatitis A and C serology, immunity to hepatitis B due to prior vaccination, negative Epstein-Barr virus infection, negative cytomegalovirus infection, negative herpes simplex virus and prior immunity to varicella virus. After ruling out viral and common toxin-induced aetiologies, penicillin was discontinued on the second day of admission. The day following discontinuation of penicillin, the patient's AST dropped to 1805, ALT to 2971 and total bilirubin had lowered to 1.8 mg/dL (figure 1). The following day, the transaminases further dropped to AST 836, ALT to 2345 and total bilirubin was 1.4 mg/dL. Since the patient's liver function tests improved, liver biopsy was deferred. As the patient was completely afebrile and asymptomatic, and his transaminases were down trending, he was discharged feeling well on day 4, to be followed up with his ophthalmologist and gastroenterology.

OUTCOME AND FOLLOW-UP

The patient's left eye ocular symptoms of blurry vision resolved completely at 2 weeks. He was feeling well and his liver enzymes had normalised at 1-month follow-up visit. The Roussel Uclaf Causality Assessment Method (RUCAM) was calculated and revealed a score of 9, suggesting 'high probability' that the offending drug that caused the liver injury was penicillin.

Figure 1 Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin levels in our patient during admission. Penicillin was discontinued on day 1 after admission.

DISCUSSION

Penicillin, both oral and parenteral administration, has rarely been associated with hepatic injury, as evidenced by very few case reports in the past several decades.² The semisynthetic penicillin derivatives, including amoxicillin, oxacillin, carbenicillin and ampicillin, more commonly produce jaundice or laboratory evidence of hepatic injury.² This is due to their synthetic nature causing development of immunological reactions that lead to liver injury. In cases of severe allergic penicillin reactions, mild elevations of serum transaminases or ALP without jaundice are common; however, the liver injury is often insignificant compared to the allergic reaction (rash, fever, facial oedema, anaphylaxis).³ Other than the mild liver injury associated with hypersensitivity reactions, the rare case reports of penicillin-induced liver injury have involved either immunologically-derived cholestatic hepatitis or transient, asymptomatic transaminitis with prolonged high doses of parenteral penicillin.⁴ Prolonged oral or parenteral high doses of penicillin have rarely been linked to liver injury and should therefore be used with caution.

A case report from 1967 described a 19-year-old patient who developed headache and nausea, followed by jaundice, fever and a generalised skin rash after taking 200 000 units of oral penicillin for a sore throat.⁴ Laboratory studies showed raised AST, alkaline phosphatase and bilirubin, and a liver biopsy showed cholestasis, and moderate lymphocyte and eosinophil infiltrations consistent with a pattern of immunoallergic cholestatic hepatitis.⁴ An often cited case report from 1974 describes a 42-year-old man who developed fever, arthralgias and mild alkaline phosphatase elevations, similar to a serum-sickness-like reaction, 8 days after starting penicillin, with liver biopsy showing unrest and focal necrosis.⁵ A case report from 1995 describes a transient elevation in transaminases, similar to that in our case, in a 67-year-old woman with no pre-existing liver disease and negative viral serologies.⁶ The patient presented with nausea, fatigue, anorexia and night sweats following a 15-day course of penicillin V (250 mg orally three times daily) and prior penicillin G treatment in hospital.⁶ Her laboratory values showed AST of 2590 U/L, ALT 3073 U/L and total bilirubin 1.3 mg/dL, with normal alkaline phosphatase. Following discontinuation of penicillin, her liver function tests promptly normalised and her general condition improved.⁶ The most recent case found, from 1997, describes a 54-year-old patient with no pre-existing liver disease and pyogenic vertebral spondylitis who developed transient asymptomatic elevation in aminotransferases (ALT especially, to 700 U/L) and eosinophilia (WCC $8.8 \times 10^9/L$; 13% eosinophils) 40 days after starting high-dose intravenous benzylpenicillin (5 million units intravenously every 6 hours).⁷ Following a switch to a cephalosporin, the transaminitis promptly resolved.⁷ This case demonstrates a likely pattern of penicillin-induced direct hepatic injury similar to that of oxacillin, with an asymptomatic rise in aminotransferases, which resolved with discontinuation of the offending agent. Similarly, our case followed a pattern of asymptomatic elevation of transaminases (especially ALT to a level of a high in the 2000–3000s) that promptly improved following discontinuation of penicillin. Furthermore, our patient had a similar pattern of normal alkaline phosphatase, only slightly elevated bilirubin and no jaundice, pointing to a direct hepatic injury versus a cholestatic pattern of injury.

In conclusion, this case report represents a rare case of relatively asymptomatic, impressive transaminitis in a patient who was recently started on high-dose parenteral penicillin. The

patient did drink 12 units of alcohol per week, but this was spread out during the week where he would drink one glass of wine with dinner on most days of the week. It is unlikely that the patient had liver injury secondary to alcohol use, since it was less than the recommended weekly allowance of 14 units per week. Of note, the patient also did not have any prior history of liver disease, confirmed by the normal serum

albumin and coagulation studies. The prompt resolution of his transaminitis following penicillin discontinuation strongly favours penicillin-induced liver injury. This case further supports the suspicion of the rare hepatotoxicity of penicillin. In these cases, discontinuation of penicillin can promptly resolve the liver injury.

Learning points

- ▶ Antibiotics are the leading cause of non-acetaminophen drug-induced liver injury, followed by non-steroidal anti-inflammatory drugs and anticonvulsants.
- ▶ The most frequently implicated antibiotic is amoxicillin-clavulanate.
- ▶ Penicillin is more commonly associated with hypersensitivity reactions and only rarely has been associated with hepatic injury.
- ▶ Discontinuation of the offending agent, penicillin in our case, can promptly resolve the liver injury.
- ▶ The Roussel Uclaf Causality Assessment Method (RUCAM) system can be calculated to determine the likelihood that the hepatic injury is due to a specific medication.

Contributors JW wrote the case report. AZ edited the case report and references. SYN reviewed the case report and was also the physician managing the patient while in hospital.

Competing interests None declared.

Patient consent Obtained.

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