AUGMENTIN-INDUCED CHOLESTATIC JAUNDICE - A CASE REPORT

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ABSTRACT

A case of cholestatic jaundice following treatment with Augmentin is reported. The awareness of hepatotoxicity due to drug should help to avoid unnecessary invasive procedures in the evaluation of this reversible condition.

Keywords: *cholestatic jaundice, Augmentin, hepatotoxicity*

SINGAPORE MED J 1993; Vol 34: 464-465

INTRODUCTION

Augmentin, a semisynthetic, penicillin-ß-lactamase inhibitor, is a combination drug of clavulanate and amoxycillin. It has been widely prescribed in Singapore since 1983 with few adverse effects. Hepatotoxicity is rare and up to March 1990, 165 cases have been reported directly to SK Beecham (personal communication). However, recognition of this infrequent association is important in the management of patients. We report a case of reversible cholestatic jaundice following Augmentin administration.

CASE REPORT

A 55-year-old Indian foreman presented to the surgical department with acute pancreatitis following an alcohol binge. He has been taking 4-5 bottles of beer daily for the past 30 years. A known diabetic for 13 years, he has been put on insulin therapy for the last 6 years. A left kidney stone was removed 3 years ago. There was no past history of biliary colic. At presentation, his liver function tests were quite normal apart from a slightly elevated gamma glutamyl transferase (GGT) of 152 u/l (normal <80 u/l). Ultrasonography as well as computed axial tomography of the abdomen showed a normal liver with no biliary tract dilatation or gall stones but a bulky pancreas which had patchy areas of decreased attenuation compatible with acute pancreatitis. His serum cholesterol, triglyceride and calcium levels were normal. He was treated with bowel rest, intravenous gentamicin 60 mg 8 hourly, metronidazole 500 mg 8 hourly, ranitidine 50 mg 8 hourly and sublingual buprenorphine 0.2 mg tds prn.

He improved gradually but had prolonged ileus and delirium from day 3. After a psychiatric review, he was started on librium 10 mg tds and diazepam 3 mg bd and 10 mg at night from day 5. He became drowsy and more confused and diazepam was reduced to once a night.

One day 10, he was seen by a hepatologist for query hepatic encephalopathy. He had fever, a raised white count, clinical and radiological evidence of a left basal pneumonia. He was taken off metronidazole, gentamicin, librium and diazepam and started on intravenous Augmentin 1.2 gm tds and chest physiotherapy. Coffee ground gastric aspirate was noted and gastroduodenoscopy confirmed acute haemorrhagic gastric erosions. There was however no hypotension or evidence of disseminated intravascular coagulopathy.

The blood and sputum culture results were negative. His sensorium improved and he responded to antibiotic treatment. The diabetes was well controlled.

However, on day 16 (day 6 of Augmentin therapy) he became jaundiced and serum bilirubin rose to 69 umol/l (N<33) with conjugated fraction of 51 umol/l, alkaline phosphatase (SAP) of 324 u/l (N<125), aspartate transminase (AST) of 56 u/l (N<40) and GGT of 358 u/l (N<80). There was no fever or tender hepatosplenomegaly. Tests for hepatitis A and B markers, antinuclear factor, anti-mitochondrial antibody and anti-smooth muscle antibody were negative. His white cell counts improved with no eosinophilia. Repeat abdominal ultrasound study showed normal liver echogenicity with no dilatation of biliary tree.

On day 21(day 11 of Augmentin therapy) his SAP and GGT levels rose to 430 u/l and 578 u/l respectively. However, the patient was asymptomatic, his jaundice had resolved with normal bilirubin, serum AST and ALT and chest infection was resolving. Endoscopic retrograde cholangiopancreatogram (ERCP) showed no evidence of mechanical obstruction with normal common bile duct and intrahepatic ducts. A percutaneous liver biopsy was performed. Histological examination showed marked centrilobular cholestasis with feathery degeneration of the hepatocytes. Intracanalicular bile plugs were evident (Fig 1). The lobules showed a mild chronic inflammatory cellular infiltrate and Kupffer cell proliferation. The portal tracts were expanded. There was a mixed inflammatory cellular portal infiltrate accompanied by ductular proliferation and some degree of fibrosis (Fig 2). However, the interlobular bile ducts were intact. There was no evidence of bile infarcts, steatohepatitis, mallory bodies or centrilobular fibrosis.

Augmentin was thought to be the possible cause of cholestasis and was stopped. His chest infection had resolved by then and the liver function tests improved slowly without any treatment after Augmentin was withdrawn. He was discharged with ranitidine and insulin therapy. At follow up 5 weeks later, he was well and the liver function tests were normal.

DISCUSSION

Penicillins have long been recognised to cause liver injury[1-3] with native penicillins producing cytotoxic or hepatitic type of injury. This injury is usually subclinical. Recently, overt cholestatic injury has been reported though uncommon, with both native and semisynthetic ß-lactamase resistant penicillins[3-6]. Cholestatic hepatitis and less commonly acute cytolytic or mixed pattern hep-

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Fig 1 - The parenchyma showed centrilobular cholestasis with feathery degeneration of the hepatocytes. (Haematoxylin & Eosin, x 250).

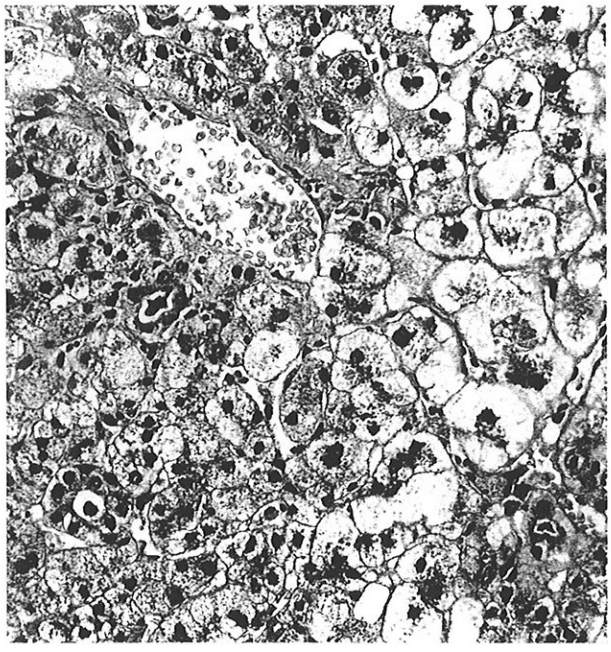
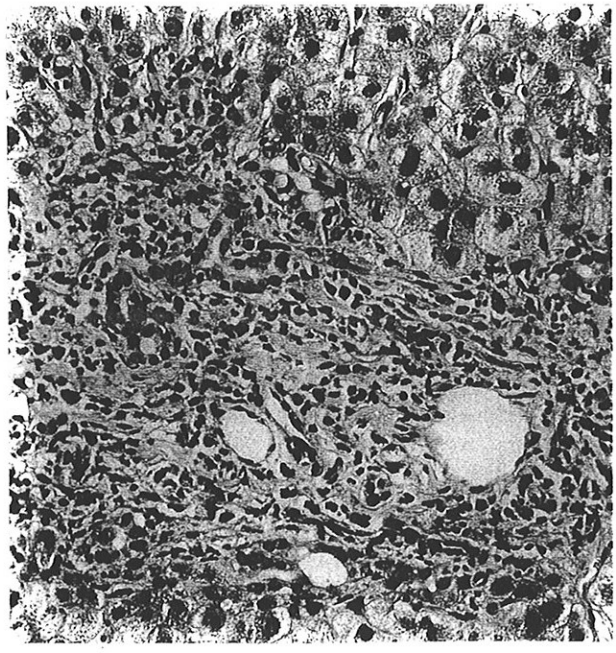


Fig 2 - The portal tracts were expanded. Note mixed inflammatory cellular infiltrate and ductular proliferation. (Haematoxylin & Eosin , x 250).



atitis due to Augmentin have also been reported[7-10]. All cases had reversal of hepatic dysfunction upon cessation of the drug. So far, there was no clinical evidence of hepatic failure in reported cases as in our patient.

The mechanism of hepatic dysfunction caused by Augmentin is unclear and unpredictable. It is probably idiosyncratic and immunologically based as in other penicillins. Fever and eosinophilia had been observed in some reports of Augmentin hepatotoxicity suggesting a hypersensitivity phenomenon[7]. Augmentin hepatotoxicity may be due either to clavulanic acid alone or to a combination of the two components though hepatic dysfunction due to amoxycillin alone is very rare[11]. Smith et al postulated that the clavulanic acid moiety is likely to be the component associated with cholestasis as rechallenge with amoxycillin had no effect on their patients who developed Augmentin hepatotoxicity[12].

Our patient had no history of penicillin hypersensitivity and had not received Augmentin previously. A causal relationship between the use of Augmentin and cholestatic liver disease within a week of receiving the drug seems highly probable. None of the other drugs which he had or disease process are likely to cause cholestatic jaundice. Jaundice due to severe bacterial infection usually showed a pattern of high conjugated hyperbilirubinemia in the presence of disproportionately low SAP which was not the case in this patient[13]. Tests for autoantibodies, hepatitis A and B were negative. No biliary tract obstruction was shown in the ultrasound study and ERCP and his SAP was rising till Augmentin was withdrawn. Although he is a heavy drinker, liver histology revealed no evidence of acute or chronic alcoholic liver disease. He recovered completely within 6 weeks of discontinuation of Augmentin. Literature review shows no documentation of predisposition of chronic alcohol ingestion to Augmentin hepatotoxicity. Advancing age, prolonged treatment may influence susceptibility and a slight male predominance was noted in previous reports[7,14]. Fever and eosinophilia documented in some cases of Augmentin hepatotoxicity were absent in our patient.

This case illustrates the necessity and importance of considering drug-associated hepatic reactions in the management of a jaundiced patient with a complicated clinical setting. Early recognition with prompt discontinuation of the offending agent will prevent further hepatic compromise, avoid invasive diagnostic procedures, ameliorate symptoms early and hasten the resolution of the illness.

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