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CASE REPORT

Flucloxacillin-induced aplastic anaemia and liver failure

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Summary

Flucloxacillin is a commonly prescribed semisynthetic penicillinase-resistant penicillin primarily used for the treatment of cutaneous staphylococcal infections. It is well-recognized that flucloxacillin may occasionally result in fatal hepatic injury. We report the case of a 40-year-old woman who developed fulminant hepatic failure and aplastic anaemia following a course of oral flucloxacillin. At the time of transplantation the patient was severely neutropenic. Post-transplant, the patient received single donor leucocyte transfusions, which resulted in a dramatic increase in neutrophil count. The patient was discharged from hospital after 120 days with normal liver function and recovered bone marrow. In this report, we discuss the care of patients with aplastic anaemia in the peritransplant setting.

Introduction

The oxypenicillins, in particular flucloxacillin, are widely used for the treatment of cutaneous infections. In Europe and Australia, this family of drugs is recognized as one of the most common causes of drug-induced liver injury [1]. It has been estimated that the risk of flucloxacillin-induced hepatitis is in the order of between 1 in 11 000 and 1 in 30 000 prescriptions, possibly less in Australia [1,2]. Flucloxacillin-induced cholestatic hepatitis is often severe and many fatalities have been reported [3].

Aplastic anaemia develops in approximately 25% of idiopathic (non-A non-B) fulminant hepatic failure after liver transplantation [4] but has not previously been linked to other forms of acute liver failure. In this report, we describe the course of a patient who developed fulminant hepatic failure and aplastic anaemia following a course of oral flucloxacillin.

Case report

In October 2001, a 40-year-old Caucasian woman was referred to our institution for investigation of jaundice and fever. In July 2001, the patient had received a 14-day course of flucloxacillin to treat a skin infection following recent ear piercing. Four weeks after starting the course of flucloxacillin she developed jaundice and pruritis. The patient had taken no other medications in the 6 months prior to the illness. She had no risk factors for viral hepatitis, no past or family history of liver disease and drank minimal amounts of alcohol.

On arrival the patient was deeply jaundiced. The liver was of normal span. She had no ascites or hepatic encephalopathy and no peripheral stigmata of chronic liver disease. There were no focal signs of sepsis. Pathology tests performed on arrival at our institution (Table 1) are as following, with normal ranges in brackets: bilirubin 638 μM (<18), alkaline phosphatase 236 U/l (35–104), alanine aminotransferase 84 U/l, γ-glutamyl transpeptidase 38 U/l (<45), international normalized ratio (INR) 0.9 (0.8–1.2), haemoglobin 82 g/l, and platelets 269×10^9 (150–400). Serological tests for acute hepatitis A, B and C were all negative. Anti-smooth muscle antibody and anti-mitochondrial antibody were negative. Abdominal ultrasound was unremarkable. Percutaneous needle core biopsy of liver showed severe acute bile stasis involving

Table 1. Laboratory parameters on admission.

Bilirubin (normal range: <18 μm)	638
INR (0.8–1.2)	0.9
Haemoglobin (115–165 g/l)	82
Platelets (150–400 × 10^9/l)	269
Neutrophils (2–7.5 × 10^9/l)	3.34
Lymphocytes (1–4 × 10^9/l)	0.64
Urea (2.5–7.7 mM)	3.4
Creatinine (0.03–0.11 mM)	0.058

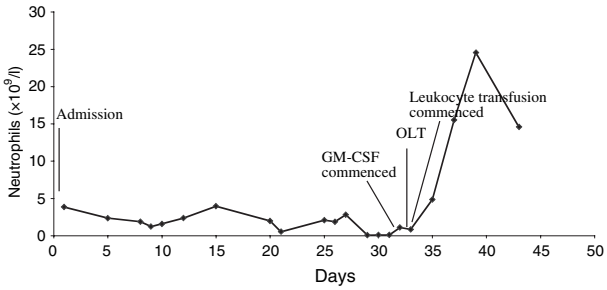

Figure 1 Graph showing neutrophil (×10^9/l) count over days. OLT, orthotopic liver transplant; GM-CSF, granulocyte–macrophage colony-stimulating factor.

acinar zone 3, and total absence of interlobular bile ducts, no bile ductular proliferation, and a sparse lymphocytic infiltrate within portal tracts. Hepatocytes were well preserved, with no significant necroinflammatory changes. The appearances were consistent with a drug-induced bile ductopenic reaction.

The patient's clinical condition was unchanged in the following week with the exception of a gradual reduction in haemoglobin, from 82 g/l on admission to 60 g/l 9 days later. There was no clinical evidence of bleeding. Tests for haemolytic anaemia were negative.

Two weeks after the admission, a bone marrow biopsy was performed to further investigate the progressive anaemia. This revealed virtual absence of red cell precursors consistent with the diagnosis of pure red cell aplasia. During this period, the patient's liver function had continued to deteriorate and she was listed for liver transplantation.

The pure red cell aplasia was treated with blood transfusion and intragam. Over the subsequent week the patient developed progressive pancytopenia. The change in the neutrophil count over days is shown in Fig. 1. Repeat bone marrow biopsy and aspirate revealed a markedly hypocellular marrow consistent with aplastic anaemia. In addition to intragam (CSL, Parkville, Melbourne, Australia), granulocyte–macrophage colony-stimulating factor (G-CSF; Amgen Incorporation, Thousand Oaks, CA, USA), and erythropoietin (Janssen-Cilag Pty Ltd, North Ryde, NSW, Australia) were commenced.

A suitable donor became available 48 days after initial admission. At this stage, the patient was in grade IV coma, on haemodialysis for renal failure and had severe pancytopenia.

Post-transplant, the aplastic anaemia was managed with human immunoglobulin G-CSF and erythropoietin in addition to daily leucocyte transfusion from a human leucocyte antigen (HLA)-matched sibling.

The post-transplant course was remarkable for the gradual reversal of the aplastic anaemia. The patient had a complicated post-transplant course before being discharged home on the 120th day post-transplant. At the last review, 2 years after transplantation, the patient was well with normal liver function and complete resolution of the aplastic anaemia.

Discussion

The development of aplastic anaemia in association with flucloxacillin-induced liver failure has not previously been reported. However, it has been well-documented in patients with non-A non-B fulminant hepatic failure [4], particularly after liver transplantation, occurring in up to 25% of such cases [5]. The explanation for the association between aplastic anaemia and non-A non-B fulminant hepatic failure remains unclear, although it has been hypothesized that it may be an as yet unrecognized virus [6].

The management of aplastic anaemia in the peritransplant period presents several unique problems. Of primary concern to us was the risk of bacterial sepsis associated with severe neutropenia. Haemoglobin and platelet counts can of course be supported by blood and platelet transfusion. The pretransplant therapy of intragam and GM-CSF factor did not result in any significant improvement in the neutrophil count (Fig. 1). On the day of transplant, the neutrophil count was just 0.17×10^9/l (normal range: $2.0–7.5 \times 10^9$). Because of concern about the potential development of life-threatening bacterial sepsis post-transplant, the patient received donor leucocyte transfusions from a HLA-matched sibling. This resulted in clinically significant increments in the neutrophil count (Fig. 1). It is possible to profile the HLA of donor and patient to determine the degree of engraftment following single donor leucocyte transfusion. We did not perform this test, as although conversion to full donor chimaerism is associated with antitumour effect in haematological malignancies, benefit in aplastic anaemia is unknown [7].

Importantly, the patient did not develop any bacterial sepsis in the immediate post-transplant period.

The previous published experience with liver transplantation in patients with aplastic anaemia has shown that a

significant percentage die from invasive fungal sepsis [8]. We suggest that all such patients should receive prophylaxis against invasive fungal infection. Published data suggests that low dose liposomal amphotericin (1 mg/kg/day), as used in this patient, is effective prophylaxis in preventing invasive fungal infection in high-risk patients after liver transplantation [9].

It might be expected that the outcome for patients undergoing liver transplantation in association with aplastic anaemia would be unacceptably poor. However, the outcome appears very similar to that of fulminant hepatic failure in general. The deaths in these patients were most frequently due to invasive fungal infections and bleeding [5].

The optimal therapy for aplastic anaemia in this setting has yet to be defined. Some authors have suggested that all patients with this syndrome should undergo immediate bone marrow transplantation [4]. However, on reviewing the more recent literature, the majority of patients recover full bone marrow function without the need for bone marrow transplantation [5], as was the case in our patient. Conventional therapy for hepatitis-associated aplastic anaemia has been to administer antilymphocyte globulin therapy [4]. It is unclear however, whether this therapy alters the natural history of the condition or whether the condition resolves spontaneously post-transplant, perhaps aided by the effects of standard post-transplant immunosuppression.

Interestingly, therapeutic use of erythropoietin has been shown to be associated with the development of pure red cell aplasia, because of the formation of erythropoietin neutralizing antibodies. Over 200 patients in Europe have been documented to have suffered this adverse event, associated with one brand of epoitin-α (marketed as Eprex and Erypo), with an incidence of 19 per 100 000 patient-years between 1999 and 2002. This disease is indistinguishable from primary pure red cell aplasia, and requires treatment with immunosuppression [10]. This is the brand of erythropioetin used in our case, however, the chronology of events shows no causality could have occurred.

In 1993, Fairley *et al.* analysed the risk factors that predispose to flucloxacillin-induced hepatotoxicity, and found that it was strongly linked to older age (>55 years) and course of therapy lasting longer than 14 days [11]. Since that time, the number of deaths from flucloxacillin-hepatotoxicity seems to have fallen in this country. A review of the Australian Drug Reactions Advisory Committee (ADRAC) database shows that in the period 1983–93 there were 26 potential flucloxacillin-related deaths (2.6 deaths/year) and from 1993 to 2003 there have been just 10 deaths reported (1.0 deaths/year), using the same method of data collection. Although the rate of deaths from flucloxacillin has fallen in recent years doctors still need to be aware of the potential for this medication to cause significant morbidity and even mortality.

The oxypenicillins have proven clinically valuable in the treatment of infections, primarily related to *Staphylococcus aureus*. However, this group of medications carries a small risk of serious hepatotoxicity, which should limit their use to situations where no alternative antibiotic drug is suitable or clinically appropriate.

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