

## Case report

### Jaundice and an itch following a fall

N Nghona, MB ChB; M W Sonderup, FCP (SA); C W N Spearman, FCP (SA), PhD

Division of Hepatology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa

Corresponding author: M Sonderup (msonderup@samedical.co.za)

#### Case report

A 34-year-old woman with no significant background history sustained a fracture of the left calcaneus requiring surgery in November 2012. A week later she developed a fever, raising the concern of osteitis. Flucloxacillin 1 g 4 times a day was started and 16 days of treatment were completed. Nausea, vomiting and diarrhoea characterised the latter stages of treatment and 4 days after completion the patient developed jaundice, followed by marked pruritus. Her initial liver profile demonstrated a mixed enzyme pattern with jaundice. Viral and auto-immune markers were negative and an ultrasound scan excluded biliary obstruction. The jaundice and pruritus became worse, and a liver biopsy was performed on day 38. It demonstrated marked cholestasis and a paucity of bile ducts (Figs 1 and 2). This was compatible with the suspected diagnosis of flucloxacillin drug-induced cholestatic liver injury, but also raised concern about the so-called 'vanishing bile duct syndrome' (VBDS).

#### Discussion

Flucloxacillin drug-induced liver injury (DILI) is well recognised, with typical clinical features including marked constitutional

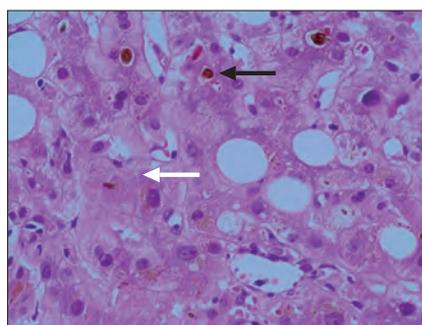


Fig. 1. High-power micrograph (H&E) demonstrating swollen degenerate hepatocytes (white arrow) and bile plugging due to cholestasis (black arrow).

symptoms, such as weight loss, diarrhoea, jaundice and intractable pruritus. It occurs in 8.5/100 000 users within the first 1–45 days of treatment and carries a mortality rate of up to 20%. Symptoms may take 6 months to resolve, with a third of patients having persistently elevated alanine aminotransferase and gamma-glutamyl transpeptidase levels for up to 18 months. Risk factors include female gender (2:1), age >55 years and duration of treatment >14 days.

Although the mechanism of injury was previously poorly understood, recent data suggest that it is both immune and

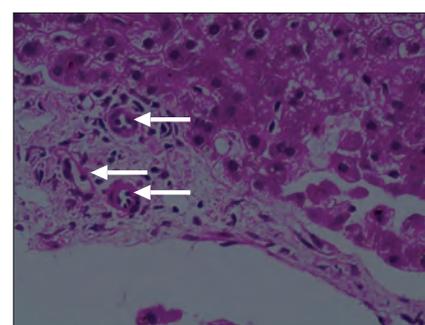


Fig. 2. Medium-power micrograph (DPAS) demonstrating a portal tract (in circle) with two branches of hepatic arteries and a single portal vein (white arrows), but no bile duct.

metabolically mediated.<sup>[1]</sup> There is a strong association with the HLA-B\*57:01 allele, with 85% of cases carrying at least one allele. Flucloxacillin binds covalently to selective lysine residues on albumin to form a hapten. Presentation by dendritic cells activates naïve CD45+ CD8+ T lymphocytes, leading to secretion of pro-inflammatory cytokines such as gamma interferon and cytolytic molecules (granzyme B, perforin and Fas-L). Activated CD8+ T lymphocytes express chemokine receptors, leading to the migration and accumulation of immune cells in the liver. The effect is an inflammatory response producing a direct liver cell injury.

Table 1. The patient's liver biochemical values

	Day								
	1*	11	20	30	35	38†	45	60	100
Total bilirubin (µmol/l)	125	142	159	192	209	197	155	68	24
Conjugated bilirubin (µmol/l)	81	81	95	113	166	164	133	54	22
Albumin (g/l)	41	36		39			41	45	45
ALP (U/l)	248	259	200	240	261	221	186	196	239
GGT (U/l)	685	240	163	215	202	164	179	223	390
ALT (U/l)	430	146	96	136	132	100	95	175	143
AST (U/l)	201	65	62	120	124	83	81	114	78
INR	1.0	0.95	1.0	1.02	1.03	1.02	1.03	0.81	0.87

\*Onset of jaundice.

†Ursodeoxycholic acid started between days 38 and 45.

ALP = alkaline phosphatase; GGT = gamma-glutamyl transpeptidase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalised ratio.

The pregnane X receptor (PXR) plays an important role in regulation of the expression of proteins involved in bile acid homeostasis. Flucloxacillin alters the expression of CYP3A4 and ABCB1, and is an agonist of the nuclear PXR. PXR polymorphism (CC genotype) has been associated with increased risk of flucloxacillin DILI.<sup>[2]</sup> The CC genotype results in lower PXR expression, and this may result in dysregulation of normal bile acid homeostasis as well as leading to higher levels of drug in the liver, thereby promoting hapten formation and immune injury. The 5'-hydroxymethyl metabolite of flucloxacillin, generated by cytochrome p450 3A4, has also been shown *in vitro* to be directly toxic to biliary epithelium.

The typical flucloxacillin DILI is cholestatic. However, in 1982 a more severe injury

characterised by progressive ductopenia was described and the term VBDS was introduced. It represents the severe end of the spectrum of flucloxacillin DILI and may progress relentlessly to cirrhosis, with liver transplantation potentially being required.

A trial of ursodeoxycholic acid (UDCA) is advised to improve the cholestasis and protect regenerating bile ductules. Our patient fortunately responded to UDCA, and her liver biochemical values have consistently improved (Table 1). UDCA has no effect on the pruritus, and given the unavailability of cholestyramine in South Africa, UVB phototherapy as advised by a dermatologist was successfully utilised.<sup>[3]</sup>

Flucloxacillin DILI is well described, and this report reminds practitioners to consider the diagnosis in patients who

develop symptoms while or after using the drug. Prompt cessation of the drug should always follow a suspected DILI.

**Acknowledgement.** Images courtesy of Professor H Wainwright, Department of Anatomical Pathology, UCT/NHLS.

### References

1. Monshi M, Faulkner L, Gibson A, et al. Human leukocyte antigen (HLA)-B\*57:01 — restricted activation of drug-specific T cells provides the immunological basis of flucloxacillin-induced liver injury. *Hepatology* 2013;57(2):727-739. [<http://dx.doi.org/10.1002/hep.26077>]
2. Andrews E, Armstrong M, Tugwood J, et al. A role for the pregnane X receptor in flucloxacillin-induced liver injury. *Hepatology* 2010;51(5):1656-1664. [<http://dx.doi.org/10.1002/hep.23549>]
3. Decock S, Roelandts R, Van Steenberghe W, et al. Cholestasis-induced pruritus treated with ultraviolet B phototherapy: An observational case series study. *J Hepatol* 2012;57(3):627-641. [<http://dx.doi.org/10.1016/j.jhep.2012.04.023>]