Drug-related biliary damage : a peculiar condition involving a genetic predisposition ?

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For the clinician, hepatic drug toxicity still remains a challenge due to its relatively high incidence especially after the fifth decade, diagnostic difficulties and unpredictable outcome. In the affected individuals, a large number of drugs known for their potential to induce hepatotoxicity may be responsible for a picture of cholestasis. Such a picture is seldom isolated and on a biochemical point of view, mixed cytolytic-cholestatic features are usually associated, even if transient. A limited number of drugs or chemical compounds may be responsible for "prolonged cholestasis", a term which qualifies the persistence of jaundice for more than six months or the continuance of biochemical cholestasis for one year or longer after the discontinuation of the therapy (1). Such a peculiar evolution is generally associated with the existence of damaging lesion to the small bile ducts which in rare cases, may eventually lead to their reduction in number or even into their disappearance, better known under the term of "vanishing bile duct syndrome" (2, 3, 4). Alternatively, other substances or chemicals given either locally or through the systemic route may cause lesions involving larger bile ducts and even the extrahepatic biliary tree mimicking those of primary sclerosing cholangitis.

In patients with small bile duct liver injury, symptoms usually occur within days after the initiation of therapy. Alternatively in some instances, they may be delayed for days or weeks after drug withdrawal as typically seen in amoxycillin-clavulanate liver toxicity. In the acute phase, the picture is generally that of an acute, often mild hepatitis, being seldom associated with features ressembling those of acute cholangitis with fever, shiver and upper abdominal pain. Extrahepatic features such as rash or erythrodermia as that often seen in carbamazepine toxicity may be superimposed. In the vast majority of patients, clinical and biochemical features vanish within 1 to 4 weeks, running a protracted course in a minority of cases which experiment "prolonged" or "chronic" cholestasis eventually but uncommonly leading to secondary biliary cirrhosis. In patients with large bile duct injury following hepatic artery infusion chemotherapy or resulting from the damaging effect of formaldehyde or hypertonic saline, features are those of a progressive cholestasis developing after months or years with or without superimposed cholangitis (5, 6, 7).

In small bile duct injury, liver histology shows in the early stages signs of cholangiolitis and/or interlobular cholangitis with various types of bile duct damage including inflammation, swelling and necrosis of biliary epithelial cells. Degenerative changes including irregularity of nuclei, vacuolisation of the cytoplasm, destruction and endothelialisation may also be seen. Ductopenia may occur culminating in the chronic stages with or without a complete disappearance of interlobular ducts together with a variable degree of inflammation and mild portal fibrosis. Neoductular proliferation is often associated (4, 8). Drugs responsible for acute cholangitic hepatitis have been subjected to a number of reviews (1, 2, 4) and encompass compounds from different classes such as neuroleptics (phenothiazines), antidepressants (amitryptiline), anticonvulsivants (carbamazepine), antibiotics (flucloxacillin, amoxycillin-clavulanic acid), lipid-lowering agents (fenofibrate), antidiabetic agents (tolbutamide, chlorpropamide) and non-steroidal antiinflammatory drugs.

Factors involved in the progression and in the pathogenesis of drug-induced bile duct injury remain largely unknown. The mechanism responsible for the acute episode of hepato-cholangitis shares a number of similarities with that implicated in the so-called immuno-allergic hepatitis. In this condition it is believed that liver cell peptides modified by the covalent binding with reactive metabolites, i.e. "alkylated" peptides, act as immune targets (9). Since the presentation of immunogenic peptides by class II HLA molecules might represent the first step of an auto- immune damage, a particular HLA haplotype may be involved. A strong argument favouring such a hypothesis has been recently brought by a Belgian collaborative study investigating a large group of patients with amoxycillin-clavulanic acid induced hepato-cholangitis. In this study in which HLA-DR and -DQ were typed using a sensitive polymerase chain reaction, reverse dot blot assay showed a strong and statistically significant association between drug-induced cholestasis and the DRB 11501 - DQbeta10602 haplotype (10). This observation, even if other events are likely to play a role in the effector phase of the process, strongly suggests

that the destruction of the small bile ducts is triggered by an immune-mediated mechanism.

Apart from that of chronic cholestasis, therapy of drug-induced small bile duct injury has been disappointing. Corticosteroids have been invariably ineffective and ursodeoxycholic acid has been shown effective only in a few anecdotal observations.

In conclusion, in the recent years a number of drugs have been recognized as potentially responsible for the occurrence of a picture of hepato-cholangitis of uncertain evolution and which may eventually lead to the so called "vanishing bile duct syndrome". This condition is increasingly recognized as involving a genetic predisposition and an auto-immune pathogenesis. When prescribing drugs which have been implicated in such drug induced liver toxicity, clinicians should be aware of this potentially severe side effect of unpredictable occurrence and outcome.

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