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LETTER TO THE EDITOR

Low N-acetyltransferase 2 activity in isoniazid-associated acute hepatitis requiring liver transplantation

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Isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) are all widely used as first-line multidrug therapy for tuberculosis. Two of these drugs, INH and PZA, carry a significant risk of hepatotoxicity. The powerful CYP450 enzyme inducer RIF may enhance toxicity of the other two, especially INH [1,2]. While drug-induced hepatitis during antituberculous treatment is frequent and potentially severe, screening options of patients at risk for severe complications like acute liver failure are limited.

A 48-year-old female patient originating from Morocco was transferred to our intensive care unit with subacute hepatic failure. Seven weeks earlier, antituberculous therapy including INH, PZA and RIF had been initiated because of a specific pleuritis. Aspartate- and alanine aminotransferase levels were 1.112 U/l and 1.005 U/l, respectively (normal 10–35 U/l); total bilirubin 18.4 mg/dl (<1 mg/dl). Coagulation parameters were: INR 4.47, partial thromboplastin time 71.6 s (25–38), and factor V 21% (70–130%). Additional laboratory examinations revealed a mild microcytic anaemia, leukopenia, and slight thrombocytosis. Ammonia increased from 69.3 μmol/l to 220.3 μmol/l (11.3–48.2). Studies for infectious agents were all negative. Ultrasound as well as computed tomography showed echo-intense homogeneous liver parenchyma with normal perfusion and absence of focal lesions. Repeated ultrasound controls demonstrated constant organ size. However, hepatic encephalopathy progressed rapidly. Therefore, orthotopic liver transplantation was performed on day 10 after transferral to the intensive care unit.

The macroscopic aspect of the explanted organ was consistent with acute toxic liver failure and histological examination supported drug-induced hepatotoxicity (Fig. 1). Unexpectedly, epithelioid cell granulomatous inflammation with central necrosis was present in a lesion that was previously undetectable by diagnostic imaging (Fig. 2). This finding was consistent with a hepatic tuberculosis lesion despite the inability to detect acid-fast bacteria. The leading cause of the acute liver failure appears to be drug-induced hepatotoxicity consistent with the overall clinical course as well as the histopathological findings.

The patient was tested for gene variants within the genes coding for major antituberculous drug-metabolizing enzymes (Table 1). Within the N-*acetyltransferase 2 (NAT2)* gene she was heterozygous for the two gene variants C481T and G857A, also referred to as NAT2*5A and NAT2*7A/B haplotypes. This genotype is well consistent with an impaired NAT2 activity. In addition, a mutation was detected within the *multidrug resistance 1* (*MDR1*) gene indicating reduced protein activity.

After liver transplantation, the patient recovered well and antituberculous treatment was continued with ethambutol, ofloxacin and streptomycin. While immunosuppressive therapy was initiated with mycophenolate mofetil, tacrolimus and methylprednisolone, there was no evidence for dissemination of tuberculosis during the subsequent 6 months of follow up.

Drug-induced hepatitis may become evident in two ways: An early increase in serum transaminase activity within the first 2 weeks of treatment (generally good prognosis) and a late increase after 1 month (poorer prognosis) [3,4]. In a recent review, about 1% of compliant patients receiving INH experienced hepatotoxic side-effects and the case fatality rate in these patients was 5% [1]. Symptoms range from asymptomatic elevation of serum transaminase levels to fulminant liver failure. Several cases of INH-associated acute hepatic failure requiring liver transplantation have been reported [5–8]. Hepatotoxicity is predominantly dose-dependent, but drug hypersensitivity also plays a role [2]. Hepatic metabolization of INH involves mainly two enzymes: the N-acetyltransferase 2 (NAT2) acylates INH to acetyl isoniazid followed by hydrolysation to acetylhydrazine and oxidation by cytochrome *P*450 2E1. Genetic variants have been found to influence NAT2 activity. While some variants increase its activity, others have been associated with slow enzyme activity. Recently, these so-called slow acetylators have been attributed a higher risk of antituberculous drug-induced hepatotoxicity [9,10]. The geographic distribution of NAT2 variants has been well characterized with the prevalence of slow acetylators being comparatively high in Europe, northern Africa and southern Asia [11,12]. However, the role of INH-metabolizing enzymes in drug-induced hepatotoxicity has not finally been cleared not only because of the several enzymes involved

Table 1. Analysis for genetic variants within INH-metabolizing enzymes.

Gene	Drug metabolism	Gene variants analysed	Patient genotype	Resulting gene expression
Glutathion-S-Transferase (GST)-genes				
GST-Ml-gene	INH	Deletion	wild type	normal
GSr-77-gene		Deletion	wild type	normal
GST-Pl-gene		I105V	wild type	normal
N-acetyltransferase 2 (NAT2)	INH	C481T (NAT2*5A)	heterozygous	reduced
		G590A (NAT2*6A)	wild type	normal
		G857A (NAT2*7A/B)	heterozygous	reduced
Multidmg resistance 1 (MDR1)	RIF	nt3435C/T	heterozygous	reduced

Findings consistent with reduced NAT2-actlvity indicating slow acetylation (*NAT2*-mutations) as well as moderately reduced MDR1-protein activity.

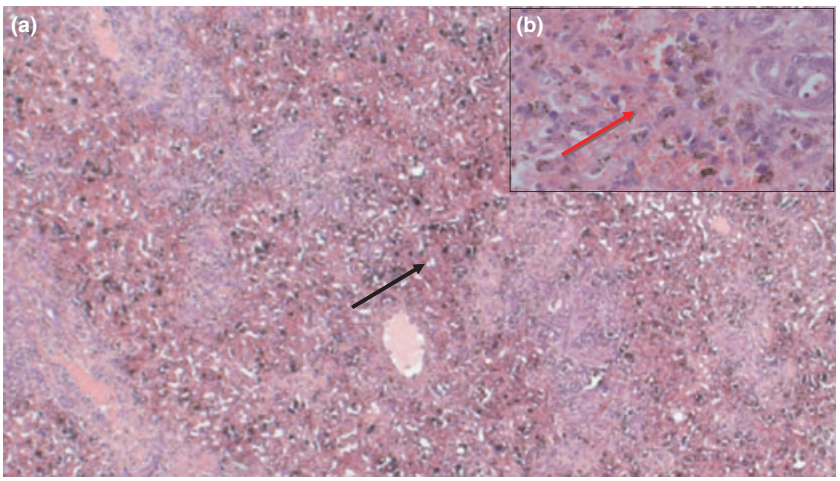

Figure 1 Extensive chronic tissue damage of the liver parenchyma compatible with drug-induced hepatotoxicity. (a) Vast abolishment of the normal parenchymal architecture in the liver with hepatocyte necrosis, haemorrhages and deposits of lipofuscin pigmentation pronounced in acinar zone 2 and 3 (red/brown) (black arrow); (b) preserved portal fields with chronic inflammation and proliferation of bile ducts (acinar zone 1) (red arrow).

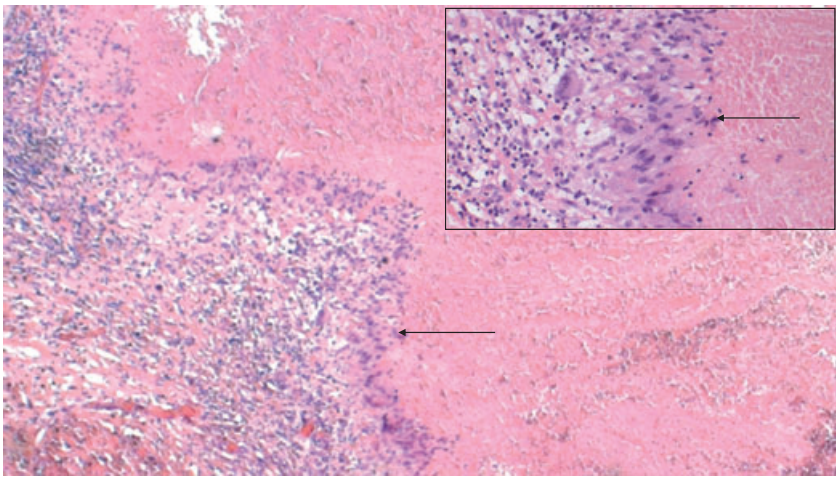

Figure 2 Epithelioid cell granulomatous inflammation with central necrosis in the liver without microscopic detection of *M. tuberculosis* consistent with a hepatic tuberculosis lesion. Chronic granulomatous inflammation with caseous necrosis and surrounding epithelioid cells, Langhans giant cells and lymphocytes corresponding to a tuberculous granuloma. There was no proof of acid-fast bacilli after Ziehl-Neelsen staining.

in INH detoxification as well as, high and yet increasing numbers of gene variants, but also because of varying definitions for INH-associated hepatotoxicity in different studies [13]. In our patient, an additional gene variant was found within the *MDR1* gene consistent with moderately impaired protein activity. MDR-1 functions as intestinal transporter protein for RIF. Both gene alterations may be related to the acute liver failure by potentially influencing serum levels of INH and RIF.

Despite the fact that she received a genetically different allograft with potentially normal NAT2 enzyme activity, the application of alternative antituberculous drugs with lower hepatotoxic potential is indicated to prevent damage to the transplanted organ. As in our patient, antituberculous treatment with ethambutol, fluoroquinolones like ofloxacin or ciprofloxacin and streptomycin has been well tolerated in other patients after liver transplantation [e.g. 6,7]. Hepatotoxic and nephrotoxic potential

of immunosuppressive drugs as well as interactions with RIF have to be taken into account.

General recommendations to prevent drug-induced hepatitis in antituberculous treatment include i) avoidance of PZA and INH in patients with underlying liver function test abnormalities, ii) initiation of treatment with INH and PZA at lowest possible dosage, iii) control of serum transaminase levels every 2 weeks within the first 2 months after antituberculous therapy was initiated, and iv) stop treatment with INH, PZA and RIF when transmanisase levels increase more than threefold above the upper reference limit. After serum transaminase levels decreased to normal, isoniazid (without RIF) but not PZA may be re-started at low dose. Ethambutol and streptomycin may be used alternatively although the latter is well known to be nephrotoxic [3].

It may be advisable to intensify controlling for drug-induced hepatotoxicity in predefined patients with increased risk like higher age, female gender, malnutrition, chronic inflammatory liver damage (e.g. autoimmune hepatitis), viral infection (e.g. CMV, EBV, HIV and chronic viral hepatitis), alcoholism, and underlying elevated liver enzymes [2,14,15]. In addition, interactions with other drugs involving the CYP450 system have to be taken into account. In high-risk patients, pretreatment genotyping for gene variants associated with disturbed drug metabolism and -detoxification in the liver may be effective. This would have to be evaluated in large clinical trials. In our patient, however, none of these known risk factors except for female gender was present.

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