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Case report

Natalizumab-induced hepatic injury: A case report and review of literature

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ABSTRACT

Natalizumab is an α4-integrin monoclonal antibody used for treatment of relapsing multiple sclerosis (MS). At least and nearly 30 cases of liver failure in natalizumab-treated patients are listed in the post-marketing FDA adverse event reporting system (FAERS) and twelve patients with severe liver injury, including several after the first infusion, have been reported (Lisotti et al., 2012; Bezabeh et al., 2010; Martinez-Lapiscina et al., 2013; Michael et al., 2007; Hillen et al., 2015). Herein, we describe a case of a young woman with relapsing MS who developed acute liver injury after the second infusion of natalizumab. Liver biopsy demonstrated a mixed pattern of medication-induced injury or partially treated auto-immune hepatitis. Liver function normalized after natalizumab discontinuation and a subsequent liver biopsy showed resolution of hepatitis. The patient's MS has since been successfully treated with rituximab for over a year. We review the published cases of liver injury associated with natalizumab and those in the post-marketing FDA adverse event reporting system (FAERS).

1. Introduction

Natalizumab is a monoclonal antibody that binds to integrin-4 expressed on the surface of activated immune cells thereby blocking their adhesion to VCAM-1 receptor on endothelial cells and inhibiting their migration into CNS. In addition, natalizumab has diffuse effects on immune function that include sequestration of all major immune cell types in peripheral circulation (Mellergård et al., 2013); mobilization of hematopoietic stem cells from bone marrow; restriction of T-cell receptor repertoire in CSF (Warnke et al., 2013); down-regulation of micro-RNA that are involved posttranscriptional regulation of gene expression and others.

Although natalizumab is not metabolized by the liver and does not appear to impact entry of immune cells into this organ (Ala et al., 2003), at least 12 cases of severe liver injury, including one fatal case have been reported. In most of these cases, the liver damage was noted after the first or second infusion. Search of FDA Adverse Reaction Reporting System (FAERS) disclosed a total of 29 instance of liver failure in natalizumab-treated patients (FDA Adverse Event Reporting System (FAERS), 2004 - 2014).

We report a case of a young woman who developed severe liver injury after a second dose of natalizumab and discuss possible causes of liver injury based on two successive liver biopsy findings. We summarize the published literature on liver injury after natalizumab exposure and present results of query of the FDA adverse event reporting system that uncovered additional cases of natalizumab-induced hepatotoxicity. We also suggest practical pointers for mitigating risk of liver injury in patients who are started on natalizumab.

1.1. Case report

A 26 year old woman presented to NYU MS Care Center (New York) with severe truncal, limb and gait ataxia one year after onset of relapsing MS. MRI of the brain showed multiple Gadolinium-enhancing lesions of the subcortical white matter as well as extensive FLAIR/T2 hyperintense lesions in periventricular areas, brainstem and cerebellum. Due to the severity of her symptoms, she was administered a 5-day course of intravenous methylprednisolone concurrently with 5 courses of Plasma Exchange (PLEX) with partial improvement of ataxia. Prior to start of methylprednisolone and PLEX, she experienced transient, unexplained elevation of transaminases (AST 134 IU, ALT 345 IU) which rapidly subsided after a third dose of steroids and PLEX (ALT 45, AST 51). She was subsequently started on Natalizumab 300 mg every 28 days with marked improvement of her symptoms. Two weeks after the second infusion she developed nausea, vomiting, jaundice, and choluria. Patient denied alcohol or drug abuse and was not on any prescription medications at the time. Liver tests were remarkable for AST 1076 IU/L (N 15–56 IU/L), ALT 856 IU/L (N 11–50 IU/L), Alkaline phosphatase 165 IU/L (N 39–117), Total

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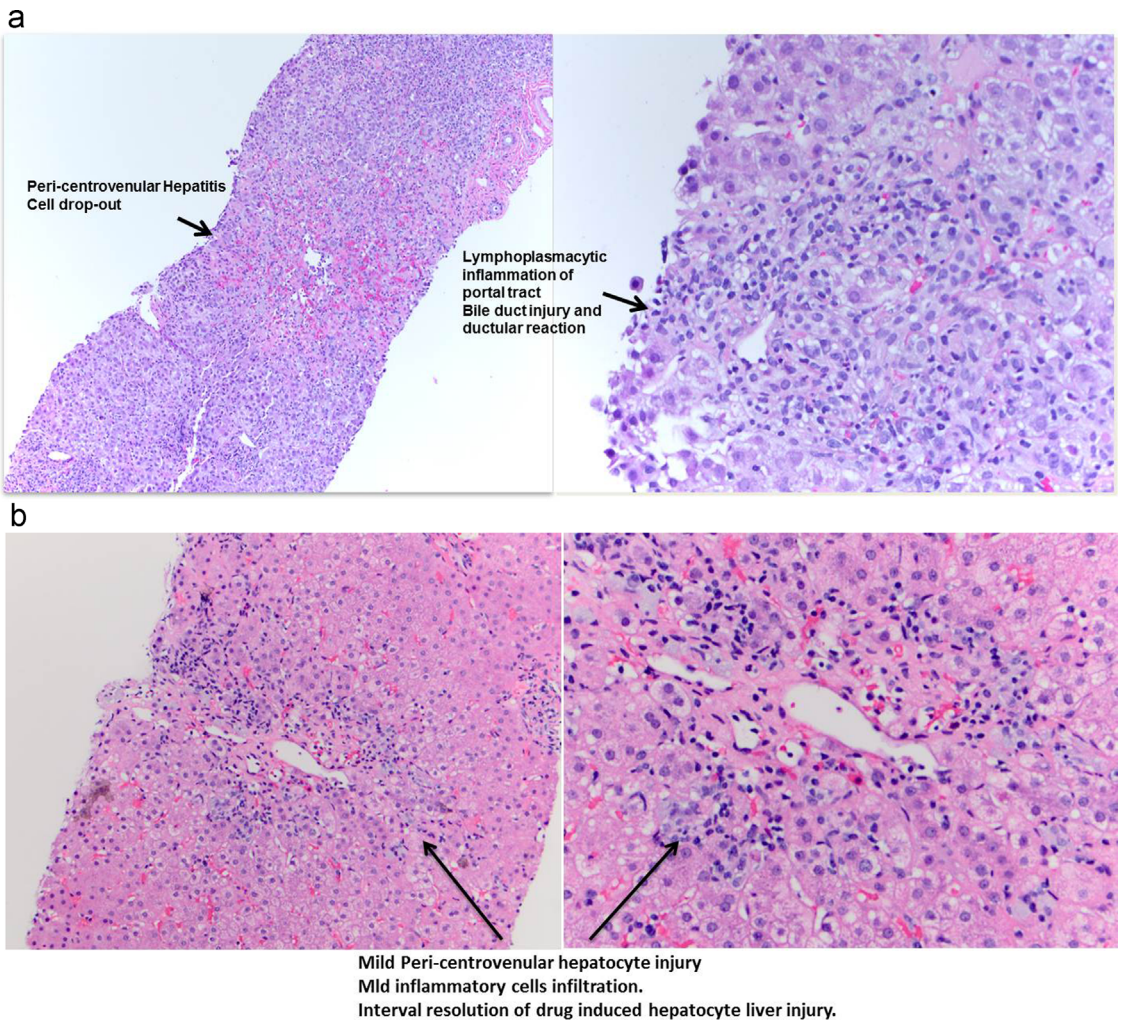

Fig. 1. a Initial liver biopsy after Natlizumab exposure. b Second biopsy 4 months after Natalizumab exposure.

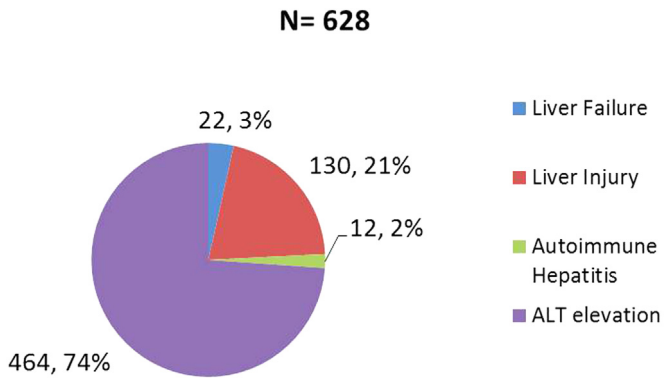

Fig. 2. Post- Marketing FDA Adverse Reaction Reporting System from 2009 to 2014.

bilirubin 24.9 mg/dl (0–1 mg/dl), conjugated bilirubin 15.7 mg/dl (0–0.3 mg/dl). Serologies for hepatitis A, B and C did not evidence recent or past infection. Anti-mitochondrial and anti-nuclear antibodies were absent, but anti-smooth muscle antibodies and F-Actin antibody were weakly positive 1:20 (normal $<$ 1:20). Liver ultrasound was negative for biliary obstruction. Liver biopsy showed signs of acute and sub-acute hepatitis with hepatocellular necrosis of zone 3, portal bridging and portal lymphocytic inflammation features consistent with drug-induced hepatocellular injury or partially treated autoimmune hepatitis (Fig. 1a) natalizumab was discontinued. Liver tests progressively normalized and, 3 months later, were only mildly elevated (AST 96 IU/L, ALT 81 IU/L, and total bilirubin 1.4 mg/dl. A second biopsy, 4 months after discontinuing natalizumab, demonstrated resolution of hepatocyte injury, mild centro-venular lymphocytic infiltration, and no signs of autoimmune hepatitis (Fig. 1b).

Patient was then started on Rituximab, off label, for relapsing MS, which she tolerated without complications for over a year.