Acute Hepatitis with Positive Autoantibodies: A Case of Natalizumab-Induced Early-Onset Liver Injury

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Patient: Female, 60-year-old
Final Diagnosis: Natalizumab-induced liver injury
Symptoms: Jaundice • pruritus
Medication: —
Clinical Procedure: Drug withdrawal
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course
Background: Natalizumab is an anti-integrin monoclonal antibody used as an alternative treatment regimen for patients with autoimmune disorders, especially multiple sclerosis and Crohn’s disease. Natalizumab-induced liver injury has been rarely reported and may follow the first dose (with increases in liver enzymes usually after 6 or more days), or after multiple doses. In general, it is non-severe acute hepatitis (with a hepatocellular pattern) and autoantibodies can be positive, mainly anti-nuclear and anti-smooth muscle antibodies.

Case Report: We are reporting the case of a 60-year-old woman diagnosed with multiple sclerosis previously treated with interferon-beta, dimethyl fumarate, and fingolimod, who presented jaundice 1 day after the first infusion of natalizumab. She had an early-onset acute hepatitis with aminotransferases levels higher than 1000 IU/L and total bilirubin almost 41 mg/dL. Anti-nuclear and anti-smooth muscle antibodies were positive and the histopathological analysis of the liver showed intrahepatic cholestasis associated with moderate necroinflammation activity (subacute cholestatic hepatitis) and mild diffuse perisinusoidal fibrosis, which could be compatible with the hypothesis of drug-induced liver injury. The scenario of an autoimmune-like hepatitis led the medical team to start oral prednisone and she progressively improved in clinical and laboratory features. Serum levels of liver enzymes and bilirubin were normal within 3 months and there was no further increase after discontinuation of corticosteroid therapy.

Conclusions: Physicians should be aware of the risk of early-onset acute hepatitis in patients starting natalizumab, especially women with multiple sclerosis. Treatment with corticosteroid for a few months may be beneficial.

Keywords: Chemical and Drug Induced Liver Injury • Hepatitis • Multiple Sclerosis • Natalizumab

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Background

Natalizumab is a monoclonal antibody with selective inhibition of the α-4 subunit of integrins. It is used as an alternative therapeutic regimen for autoimmune disorders, especially multiple sclerosis (MS) and Crohn’s disease [1,2]. Several adverse effects have already been described, such as rash, abdominal discomfort, gastroenteritis, nausea, urinary tract infection, depression, fatigue, and lower and upper respiratory tract infection. The most feared complication is progressive multifocal leukoencephalopathy, a serious neurological condition possibly associated with JC virus reactivation in the neural system [1-3].

Liver toxicity is not a common event and has an idiosyncratic autoimmune-like pattern, mainly described in subjects with MS. Most of them show signs of liver injury within 6 days following the first dose, or after multiple doses of natalizumab [1,4-6]. We report the case of a female patient who presented natalizumab-induced early-onset acute hepatitis with positive anti-nuclear and anti-smooth muscle antibodies.

Case Report

A 60-year-old woman was diagnosed with MS at age 52 and had undergone multiple therapies: 1) interferon-beta (interrupted due to skin lesions), 2) dimethyl fumarate (suspended due to drowsiness and weakness), and 3) fingolimod (withdrawn due to treatment failure). The medical staff then decided to perform pulse therapy with methylprednisolone and start natalizumab (300 mg intravenously).

On the day after the first dose of natalizumab, she reported jaundice with progressive worsening. A week later, she was admitted to the hospital with jaundice, fecal acholia, nausea, and itching. There was no fever, myalgia, diarrhea, or abdominal pain. She denied risky sexual exposure, recent trips, alcohol intake, use of illicit drugs, other medications, and herbal products. On physical examination, she was overweight (body-mass index=29.3 kg/m²) and there was no flapping or features of chronic liver disease. Laboratory test results are described in Table 1. She had non-severe acute hepatitis with a pattern of hepatocellular injury and positive anti-smooth muscle and anti-nuclear antibodies (cytoplasmic pattern). Abdominal ultrasound showed a liver with normal morphology, cholelithiasis with no signs of cholecystitis, and no dilatation of the biliary tract. During hospitalization, it was necessary to prescribe cholestyramine and hydroxyzine for pruritus.

The autoimmune hepatitis diagnostic score was 7 points (unlikely diagnosis). Therefore, the main diagnostic hypothesis

### Table 1. Initial laboratory tests.

| Blood tests       | Patient | Normal range | Immunology            |
|-------------------|---------|--------------|-----------------------|
| Hemoglobin        | 15.8    | 12-16 g/dL   | HBsAg                 |
| Leucocytes        | 11,630  | 4000-10,000/mm³ | Anti-HBc              |
| Platelets         | 154,000 | 150,000-400,000/mm³ | Anti-HBs              |
| ALT               | 1151    | <35 U/L      | Anti-HAV IgG          |
| AST               | 1790    | <35 U/L      | Anti-HAV IgM          |
| AP                | 315     | <104 U/L     | Anti-HCV              |
| GGT               | 151     | <40 U/L      | Anti-HIV              |
| Total bilirubin   | 35.9    | 0.3-1.2 mg/dL| Cytomegalovirus IgG   |
| Direct bilirubin  | 26.5    | <0.2 mg/dL   | Cytomegalovirus IgM   |
| Albumin           | 3.1     | 3.5-5.2 g/dL | Syphilis              |
| INR               | 1.27    | <1.25        | Epstein-Barr virus IgM|
| Urea              | 17      | 17-43 mg/dL  | Anti-smooth muscle AB |
| Creatinine        | 1.0     | <0.9 mg/dL   | Anti-mitochondrial AB |
| IgG               | 552     | 950-1500 mg/dL| Anti-nuclear AB       |
| Ceruloplasmin     | 45      | 20-60 mg/dL  | RT-PCR-SARS-CoV2      |

ALT – alanine aminotransferase; AST – aspartate aminotransferase; AP – alkaline phosphatase; GGT – gamma-glutamyl transferase; INR – international normalized ratio; IgG – immunoglobulin G; IgM – immunoglobulin M; HAV – hepatitis A virus; HCV – hepatitis C virus; HIV – human immunodeficiency virus; AB – antibody; RT-PCR-SARS-CoV-2 – reverse transcriptase-polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2.
was natalizumab-induced liver injury. Ten days after hospital admission, serum liver enzymes had a partial improvement: alanine aminotransferase (from 1151 U/L to 540 U/L) and aspartate aminotransferase (from 1790 U/L to 794 U/L); but there was an increase in total bilirubin levels (from 35.9 mg/dL to 40.9 mg/dL) (Figure 1). Coagulation tests and platelets count remained normal, so the medical staff performed ultrasound-guided percutaneous liver biopsy and started empirical treatment with oral prednisone 40 mg/day. She was then discharged from the hospital for outpatient follow-up.

There was a progressive improvement in symptoms and laboratory test results (Figure 1) and the dosage of corticosteroid has been progressively reduced in the outpatient follow-up. Histopathological analysis of the liver showed intrahepatic cholestasis associated with moderate necroinflammatory activity (subacute cholestatic hepatitis) and mild diffuse perisinusoidal fibrosis, which could be compatible with the hypothesis of drug-induced liver injury (DILI) (Figure 2). Liver enzymes and bilirubin levels were normal 3 months after starting oral prednisone and there was no subsequent increase after corticosteroid withdrawal.

**Discussion**

Natalizumab-induced liver toxicity is rare and may occur since the first or second dose or after multiple infusions. It is usually non-severe acute hepatitis and resolves spontaneously [1]. Time to normalization of liver parameters is variable since the
The detection of positive autoantibodies in patients with DILI is not uncommon and has been described with several drugs, including nitrofurantoin, hydralazine, alpha-methyldopa, and amoxicillin/clavulanate [8,9]. It is also possible and even frequent in patients with natalizumab-induced liver injury, and it may become negative after drug discontinuation [1,4-6]. It is important to highlight that some individuals with MS may have positive liver autoantibodies that are investigated only after a suspected event of liver toxicity [10].

Compiling the reported cases, most patients with natalizumab-induced liver injury were women diagnosed with MS and previously treated with interferon-beta, as natalizumab is used as an alternative therapeutic regimen [5,11]. Our patient was older than the mean age described (60 years vs 41 years), and her total bilirubin levels were higher (41 vs 25 mg/dL). Symptoms of liver damage started the day after the first dose (earlier than all reported cases).

Histological changes, as well as clinical, laboratory, immunological features, and the evolution are compatible with DILI. The temporal relationship between the initiation of natalizumab and the problem of jaundice (in the absence of other hepatotoxic drugs) is sufficient to establish the diagnosis of natalizumab-induced liver injury. The summary of previous reports is shown in Table 2.

Corticosteroids are generally not chosen as a treatment for DILI; however, physicians may prescribe prednisone/methylprednisolone or even immunosuppressants for a few months to shorten the recovery period [1,12], especially in an autoimmune environment, as suggested by a recent systematic review [13].

### Conclusions

Patients starting natalizumab therapy need to be informed about the symptoms of liver toxicity and failure. Since most

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**Table 2. Main features of our case and others previously published.**

| Age | Gender | Doses to the event | Days after the first dose | Previous therapies beyond CE | Antibodies | Author |
|-----|--------|-------------------|---------------------------|-----------------------------|------------|--------|
| 60  | F      | 1                 | 1                         | IFN-β, DMF, FLM             | ANA, ASMA  | Our case |
| 51  | F      | 33                | –                         | –                           | ASMA       | Martínez-Lapiscina [4] |
| 26  | F      | 2                 | –                         | –                           | ASMA       | Antezana [5] |
| 31  | F      | 2                 | –                         | –                           | ANA        | Lisotti [6] |
| 26  | F      | 1                 | Na                        | Na                          | Na         | Kader [11] |
| 52  | F      | 2                 | –                         | Na                          | Na         | Kader [11] |
| 26  | F      | 1                 | 6                         | Na                          | Na         | Bezabeh [1] |
| 43  | M      | 5                 | –                         | Na                          | ANA        | Bezabeh [1] |
| 33  | F      | 1                 | 18                        | IFN-β                       | ASMA       | Bezabeh [1] |
| 59  | F      | 1                 | 8                         | Na                          | Na         | Bezabeh [1] |
| 50  | F      | 1                 | ~14                       | IFN-β, GAC                  | ASMA, ANA, AMA | Bezabeh [1] |
| 58  | M      | 12                | –                         | IFN-β                       | Na         | Bezabeh [1] |

F – female; M – male; CE – corticosteroids, IFN-β – interferon-beta; DMF – dimethyl fumarate; FLM – fingolimod; Na – not available; ANA – anti-nuclear antibody; ASMA – anti-smooth muscle antibody; AMA – anti-mitochondrial antibody; GAC – glatiramer acetate.
cases have been reported after the first or second dose, physi-
icians should request appropriate laboratory exams and be
aware of the risk of early-onset acute hepatitis. A good recov-
ery is expected after discontinuation of natalizumab and us-
ing corticosteroids.

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