Autoimmune hepatitis in a patient with thymectomy: the benefit of histology and MUM-1 immunostaining

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To the Editor,

A 61 years-old female patient, with a history of myaesthenia gravis since 1992, for which she underwent a thymectomy and is treated by pyridostigmine 60 mg once daily, was referred to our outpatient clinic by her general practioner for symptoms of nausea, lack of appetite and pyrosis. Abdominal clinical examination and upper gastrointestinal tract endoscopy were normal. Routine biological testing showed an important liver enzyme perturbation, with a typical hepatocellular injury pattern: aspartate aminotransferase level (AST) at 1449 U/L, alanine aminotransferase level (ALT) at 1856 U/L, alkaline phosphatase level (ALP) at 211 U/L, gamma-glutamyl transpeptidase level (GGT) at 211 U/L, lactate dehydrogenase level (LDH) at 796 UI/L, total bilirubinemia was 5.85 mg/dL, direct bilirubinemia was 5.18 and ferritinemia was above 2000 ng/ml. Peripheral blood cells showed 2670 leucocytes/µL (with 46.3% of neutrophils and 25.7% of lymphocytes). Abdominal ultrasound was normal. No indirect signs of lymphoma such as splenomegaly or adenopathy were found. Hepatitis A serology was positive for IgG and negative for IgM, whereas other viral hepatitis (B, C and E) serological markers were all negative. Epstein-Barr Virus (EBV) serology showed a past history of contact/infection, with EBV IgG at 60 U/mL, EBV IgM negative. Cytomegalovirus IgM and IgG were negative. Gamma globulin levels were normal. Autoimmune antibodies were all negative. After extensive research, no contact was found with hepatotoxic substances or herbal supplements. Later on, in another lab, anti-nuclear antibodies were found positive (titer 1/640). The following days, the patient developed significant clinical jaundice (total bilirubin at 12 mg/dL and then higher than 20 mg/dL). Transaminase level remained high but stable, and international normalized ratio (INR) was in the normal range. A transvenous liver biopsy was then performed. The hepatovenous pressure gradient was 12 mmHg and liver histology showed a severe non-specific acute lymphocytic hepatitis, with only 15% of the remaining hepatocyte parenchyma (Figure 1A) without significant fibrosis at Masson trichrome staining (not shown).

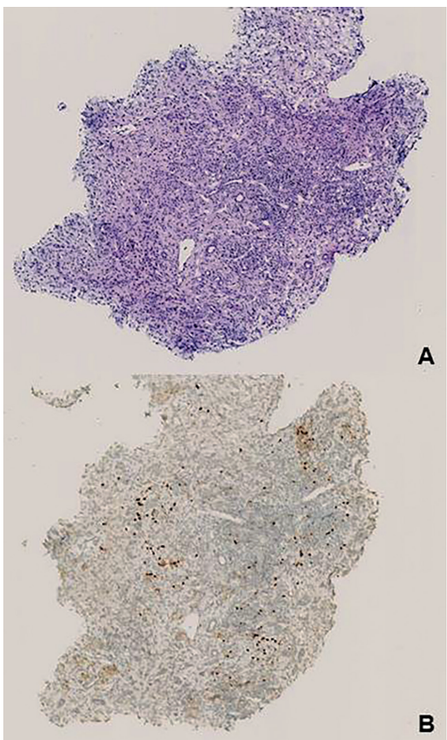

Figure 1. — Hematoxylin and eosin staining showing massive severe non-specific acute periportal interface lymphocytic hepatitis, with low remaining hepatocyte parenchyma (A). Immunostaining for multiple myeloma oncogene 1 (MUM1) showing positive plasma cells and plasma cell precursors (brown) organized in an irregular ring-like periportal location (B).

Based on this massive lobular inflammation, context of auto-immune disease (myasthenia), positivity of anti-nuclear antibody, severe life-threatening condition with low remaining viable liver parenchyma and absence of other cause, we considered the diagnosis of auto-immune

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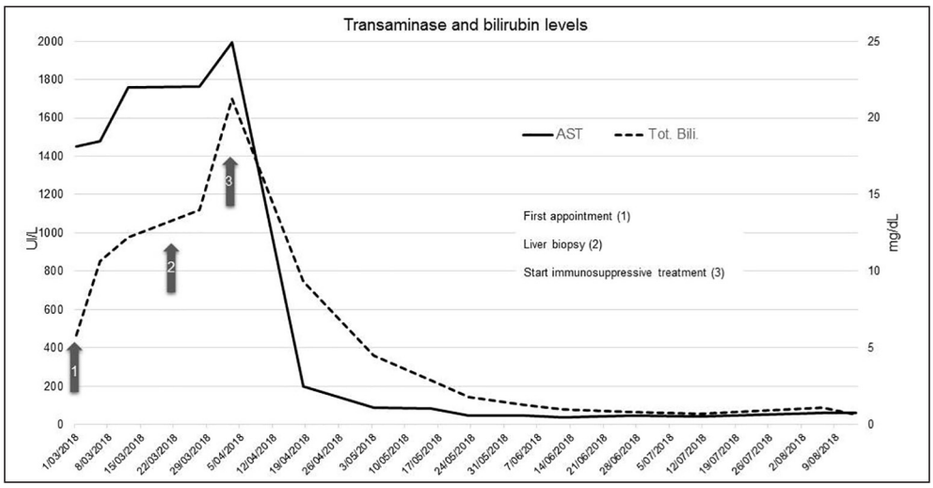

Figure 2. — Transaminase and bilirubin levels at different time-points: beginning of the symptoms (first appointment), liver biopsy, immunosuppressive treatment initiation and during patient's follow-up.

hepatitis, despite a simplified score of 5 points/8 (1). To support this hypothesis, immunostaining for multiple myeloma oncogene 1 (MUM1) was used showing irregular ring-shaped positive cells at the periphery of the portal tract (Figure 1B), in favor of an automimmune hepatitis (2). A treatment with methylprednisolone 32 mg daily was then given. Transaminase and bilirubin levels decreased abruptly following the introduction of the immunosuppressive treatment (Figure 2), thus reinforcing the diagnosis of auto-immune hepatitis. Five weeks later and after negative thiopurin methyltransferase (TPMT) deficiency mutation testing, azathioprine was initiated at a dose of 50 mg daily. Methylprednisolone was then gradually decreased with no recurrence of abnormal liver tests within a four month follow-up (Figure 2).

The removal of thymus gland (thymectomy) is indicated in cases of thymomas but also in order to reduce the level of antibodies causing the disease (myasthenia gravis). We want here to draw attention on the negativity of autoantibodies and normal immunoglobulin level despite the acute auto-immune hepatitis, a situation which was already described in another patient with thymectomy (3). In this context of coexistence of autoimmune background and acute hepatitis of unknown origin, the liver biopsy keeps a central place in order to diagnose autoimmune hepatitis and start appropriate treatment. Immunostaining for MUM-1 could help in this diagnosis.

Conflict of interest

The authors declare no conflict of interest/disclosure regarding this manuscript. There is also no financial support.

Keywords : Autoimmune hepatitis, myasthenia, histology, MUM-1, thymectomy.

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