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Autoimmune Hepatitis Triggered by Adalimumab and Allergic Reactions after Various Anti-TNFα Therapy Agents in a Patient with Rheumatoid Arthritis

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Autoimmune hepatitis (AIH) is a generally progressive chronic hepatitis of unknown cause that occurs in children and adults of all ages. Occasionally it has a fluctuating course, with periods of increased or decreased activity. The diagnosis is based on histological abnormalities, characteristic clinical and biochemical findings, and abnormal levels of serum globulins, including autoantibodies.

The anti-tumor necrosis factor-alpha (anti-TNFα) agents – such as infliximab, etanercept and adalimumab – are commonly used in the treatment of rheumatological, dermatological and gastrointestinal autoimmune disorders. To date, more than 1,500,000 patients around the world have been treated with anti-TNFα since its introduction in 1999. These anti-TNFα agents were found to be safe and effective in controlling disease activity, reducing mortality and morbidity, as well as improving quality of life. Infections, worsening symptoms in patients with established heart failure, and major or minor skin reactions are some of the observed side effects of these drugs [1]. Liver enzyme abnormalities are commonly observed in patients with rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), spondyloarthropathy and psoriasis, who are generally treated with anti-TNFα. Coincidental viral hepatitis, non-alcoholic fatty liver disease and hepatotoxic agents especially, traditional disease-modifying anti-rheumatic drugs (DMARDs), and non-steroidal anti-inflammatory drugs have been implicated as the main causes [2]. Similarly, reports of anti-TNFα-induced liver injury or AIH as complications are increasing in patients treated with these agents.

Approximately 9% of the AIH cases are triggered by drugs. According to the registry data of the BIOGEAS project (a Spanish registry collecting data on the use of biological agents in adults with systemic autoimmune diseases), prior to 2009, more than 800 cases developed autoimmune diseases associated with biological agents. While drug-induced lupus, vasculitis, optical neuritis, interstitial lung disease and inflammatory ocular disease accounted for more than 50% of new-onset autoimmune disorders, AIH also accounted for 2.0% [3].

Adalimumab – a fully human immunoglobulin G-1 (IgG1) antibody against TNF – has been previously associated with AIH induction. Infliximab was reported as the main cause in the majority of cases that developed liver injury. However, it is well known that infliximab is the first TNFα blocking agent and is thus used more commonly than either etanercept or adalimumab. In some patients with infliximab-induced hepatitis, liver injury was not observed after they switched from infliximab to adalimumab or etanercept.

PATIENT DESCRIPTION

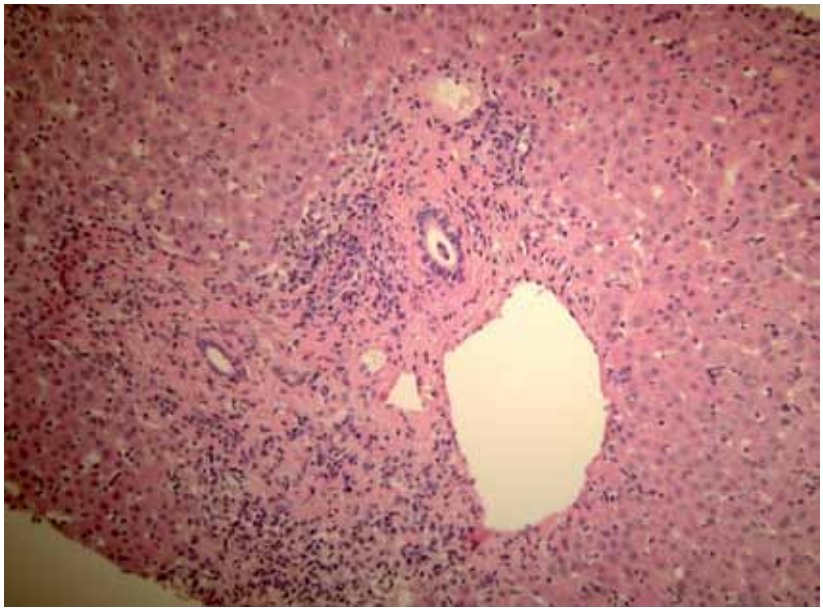
We report the case of a 33 year old Slovak woman with a history of primary Sjögren syndrome that began in 2005. At the time of diagnosis and for the next 6 years she showed positivity of ENA antibodies (SS-A as well as SS-B) and was initially treated with prednisolone 15 mg/day with a good effect. She did not have a history of allergy and a complete immunology evaluation in 2006 revealed antinuclear antibody (ANA) positivity (diffuse immunofluorescence pattern) and in 2008 anti-CCP positivity. However, in 2009, arthralgia occurred and she was diagnosed with seropositive rheumatoid arthritis.

Treatment with metotrexate was initiated but the patient did not respond well. Therefore, repeated intravenous immunoglobulin (IVIG) was instituted during the years 2009–2010. In 2010 treatment with methotrexate was again indicated, but the patient experienced dyspepsia. Later, antimalarials were indicated but their effectivity was low. DMARDs were then combined with corticosteroids. Since this had only a partial effect on the underlying disease, in September 2011 we changed the treatment to adalimumab. Clinical activity was very high: DAS28 (disease activity score) 8.41. Hepatobiliary enzymes prior to therapy were within normal limits except for slightly elevated asparate aminotransferase (AST) 44.31 U/L (normal value 10–30) and alanine aminotransferase (ALT) 43 U/L (normal 10–40), which was attributed to treatment with DMARDs. Hepatitis B surface antigen and anti-hepatitis C virus

antibody were negative. After three subcutaneous doses of adalimumab the patient developed malaise with significant liver damage. A blood test revealed AST 922.16 U/L, ALT 888.62 U/L, gamma-glutamyl transferase (GGT) 165.27 U/L (normal 2–30), and alkaline phosphatase (ALP) 348.50 U/L (normal 30–120). While serological tests for hepatitis A, B and C viruses, Epstein-Barr virus, and cytomegalovirus were all negative, her serum immunoglobulin G levels were elevated (21.98 g/L, normal 7–16) and both homogeneous and speckled-type ANAs were present. Anti-smooth muscle antibody (ASMA) and anti-mitochondrial antibody (AMA) were positive as well. DsDNA antibodies were negative. A percutaneous liver biopsy 2 weeks after discontinuation of adalimumab showed marked portal lymphoplasmacytic inflammation with evident interface hepatitis and rosetting of liver cells. No evident signs of cholestasis were present. Based on the liver biopsy the pathologist concluded that the patient had chronic hepatitis with marked necro-inflammatory changes (grade 2–3) compatible with AIH. Examples of the histological changes are shown in Figure 1.

Based on these findings we diagnosed probable AIH (this was confirmed using simplified international diagnostic criteria: score 14 points, definite AIH ≥ 15) [14], and she was treated with 40 mg prednisolone per day (0.75 mg/kg/day is the standard initial therapy regimen for AIH) for 2 weeks with the reduction of the dose by 10 mg every 2 weeks. The maintenance dose was set at 10 mg per day. A month later, her hepatobiliary enzymes returned to normal. While the patient was still under maintenance therapy, there was no relapse of AIH. However, since clinical and humoral inflammatory activity of RA was still high, we decided, 4 months after stopping adalimumab, to introduce another anti-TNFα agent (etanercept) into the therapy. Within a month of etanercept treatment the patient developed an allergic reaction with severe pruritus of the skin and redness at the site of injection and this treatment was discontinued. Basophil degranulation test was positive for etanercept. Another anti-TNFα agent, certolizumab pegol, also failed because of the patient's allergic reaction. Certolizumab pegol is a monoclonal antibody directed against TNFα. Finally, anakinra, an interleukin-1 receptor antagonist, was successfully introduced into the therapy and the patient has been doing well for more than 18 months. Clinical activity of RA is DAS28 2.78, and there are no side effects with this biologic agent. With maintenance therapy of 10 mg prednisolone throughout the course of anti-TNFα agents her liver enzymes are within normal limits.

Figure 1. Portal tract showing mild to moderate chronic inflammation, with focal interface hepatitis (upper left and lower left part of the portal tract)



COMMENT

AIH is an idiopathic chronic progressive hepatitis affecting children and adults of all ages. The disease presentation resembles that of other forms of chronic hepatitis, with common features of fatigue, right upper quadrant pain, jaundice, pruritus, and arthralgias. Histologic features on liver biopsy show periportal hepatitis with lymphocytic infiltrate, plasma cells, and piecemeal necrosis. A lobular hepatitis can also be observed. The pathologic mechanism in AIH is postulated to be loss of tolerance to the liver. This process is thought to be mediated by CD4+ T lymphocytes. Hepatocytes pathologically express human leukocyte antigen class II molecules and are destroyed by activated inflammatory cells or via an autoantibody-mediated process.

Some 20 cases of AIH triggered by anti-TNFα therapy have been reported to date. The median time to the onset of liver damage is 2 months, with three median doses of anti-TNFα drugs. All cases discontinued anti-TNFα therapy after the onset of liver damage and six were treated with a corticosteroid with or without azathioprine. All cases exhibited a good response to the therapies and a favorable prognosis; the liver damage was resolved within approximately 3 months in most cases. To date only one case of severe cholestatic liver damage after adalimumab therapy has been reported; this patient had Crohn's disease.

Because of a shared autoimmune mechanism, diverse forms of autoimmune diseases may develop in the same patient. The mosaic of autoimmunity has been proposed to describe this concept. Moreover, a patient with autoimmunity may have concomitant allergies. In a large study in

Canada, a history of allergy was positively related to the prevalence of RA in both women and men (adjusted odds ratio and confidence interval 1.57 and 1.43–1.73 in women, and 1.55 and 1.36–1.77 in men) [5]. One study evaluated liver biopsies of drug-induced liver injury (DILI) and AIH patients, but no single indicative histological feature could be found for either AIH or DILI. These findings showed that there are no pathognomonic features to distinguish AIH from drug induced-AIH or DILI since clinical, biochemical, serological, and histological patterns may be similar in all these conditions.

This was also the case in our patient who had ANA positivity before the onset of AIH as part of the immunological profile of RA. Only after starting anti-TNFα therapy did she develop hepatic injury, exhibiting ASMA and AMA positivity. Moreover, the diagnosis of AIH was also confirmed by liver biopsy. Unfortunately, she had an allergic reaction to another two anti-TNFα agents and tolerates only interleukin-1 receptor antagonist. Seropositivity for ANA can develop after anti-TNFα treatment or may be associated with an underlying disease such as RA. Therefore, ANA positivity alone is insufficient to diagnose AIH in patients treated with anti-TNFα. In these patients, relapses after discontinuation of an immunosuppressant, the presence of more specific antibodies such as anti-smooth muscle, soluble liver antigen, or a combination of two antibodies are more suggestive of real AIH.

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