

Crohn's disease of the small bowel, complicated by primary biliary cirrhosis, Hashimoto thyroiditis, and Raynaud's phenomenon: favorable response of all disorders to adalimumab treatment

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ABSTRACT

We describe the case of a male patient suffering from long-lasting Crohn's disease of the small bowel who developed thyroiditis Hassimoto, Raynaud's phenomenon, and primary biliary cirrhosis, during the course of the underlying bowel disease. It is not clear whether these co-morbidities appeared coincidentally, or because they share some common immunopathogenetic mechanisms. In this patient, Crohn's disease favorably responded to the treatment with an anti-TNF- α agent (adalimumab). The serum titers of antimitochondrial antibodies and cholestatic enzymes considerably reduced during the 3-year treatment with the biologic agent. Raynaud's phenomenon, also, completely disappeared. Bearing in mind the possible involvement of TNF- α in the pathogenesis of primary biliary cirrhosis, it could be argued that the clinical and laboratory improvement of liver disease, as well as the reduction in serum titers of antimitochondrial antibodies, might be due to the anti-TNF- α action of adalimumab. We suggest that it would be worth further investigating the role of biologic agents in the treatment of patients with primary biliary cirrhosis.

Keywords: Crohn's disease, Primary biliary cirrhosis, Extraintestinal manifestations, Inflammatory bowel disease, Infliximab.

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Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by the development of autoantibodies (AMA) directed against mitochondrial components, antibodies against nuclear components, such as anti-Sp100 and anti-gp 210, and by progressive destruction of the intrahepatic bile ducts, resulting in fibrosis, cirrhosis, and finally liver failure (1,2). Tumor Necrosis Factor- α (TNF- α) might be related to

both the severity and prognosis of patients with PBC (3).

Crohn's disease (CD) is frequently associated with a number of extraintestinal manifestations. Many hepatobiliary disorders could complicate its course, with some of them, including autoimmune thyroiditis (4), harboring immunological mechanisms in their pathogenesis.

The treatment of CD with anti-TNF- α agents has dramatically changed the outcome of the disease. On the other hand, the treatment of PBC is mainly symptomatic aiming to restore the

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increased levels of cholestatic liver enzymes, and reduce the severity of clinical symptoms.

The association of PBC with CD is extremely rare (5). We describe herein the case of a male patient with long-standing CD who developed autoimmune Hashimoto thyroiditis, PBC, and Raynaud's phenomenon, during the course of long-standing CD of the small bowel. In this patient, the underlying CD, and the accompanying PBC and Raynaud's phenomenon, favorably responded to adalimumab administration.

Case Report

A male patient, aged 48, was admitted in our department in 2009, complaining mostly of diarrhoea, loss of weight, fatigue, and arthralgias. The family history revealed that his son, aged 17, was suffering from CD of the large bowel accompanied by extraintestinal manifestations (arthritis). His mother was suffering from systemic lupus erythematosus, while his sister from Sjogren's syndrome.

From his past history, he mentioned CD of the small bowel accompanied by perineal fistula, diagnosed in 1994. Two years after the establishment of diagnosis of CD, he underwent total thyroidectomy because of hyperthyroidism were not responding to conservative treatment. The histology of the surgical specimen revealed that hyperthyroidism developed on the ground of thyroiditis Hashimoto.

In the subsequent years, CD was running with exacerbations of mild to moderate severity that promptly responded to oral administration of steroids and mesalamine. The patient did not receive azathioprine because of serious side-effects. In 2004, because of a severe flare-up of the disease he was treated with infliximab 5mg/Kg BW. Although the biologic agent resulted in favorable clinical and laboratory effects, it was interrupted after 4 sessions, because of the appearance of high fever attributed to the drug

itself. At that time, an abdominal CT scan revealed liver enlargement and a thickness of many loops of both jejunum and ileum.

On admission in our department in 2009, the laboratory investigation revealed ESR 85 mm, Hct 35.1%, Hb 11.8g/dl, fibrinogen 517 mg/dL (n.v. 200-400), CRP 26.5 mg/L (n.v. <3). iron 43 µg/dl (n.v. 60-160), Ferritin: 29.4 ng/ml (n.v. 25-280), vitamin B12 489 (n.v. 200-600) folic acid 20.7 ng/ml (n.v. 3-16), transferrin 301 mg/dl (n.v. 200-400), and transferrin saturation 10.2% (n.v. 15-50). Renal function tests, serum amylase, serum albumin, serum electrolytes, and tumor markers were normal. Serum lipids were as follows: Cholesterol 264 mg/dL (n.v. <200), HDL 56 mg/dL (n.v. >40), LDL 178 mg/dL (n.v. <160), and triglycerides 151 mg/dL (n.v. <150). Hepatitis B and C serum antibodies, p-ANCA, c-ANCA, anti-MPO, anti-PR3, anti-endomysium, anti-gliadin (G & A), and anti-tTG (G & A) were negative. However, anti-TG, anti-nuclear, anti-mitochondrial, antimitochondrial and anti-M2 serum autoantibodies revealed significantly higher values above the normal limits [2700 IU/ml (n.v. <200), 1:640 (n.v. 1:80), 4100 IU/ml (n.v. <100), 1:360 (n.v. <1:40), and 75.4 U/ml (n.v. <15) respectively]. Serum IgG was 1560 mg/dl, IgA 290 mg/dl (n.v. 70-400), and IgM 250 mg/dl (n.v. 40-230). Serum inflammatory indices, including CRP and α1-acid-glycoprotein, were increased [36 mg/L (n.v. <3) and 1.61 g/L (n.v. 0.5-1.2), respectively]. The patient denied liver biopsy. Abdominal MRI revealed no abnormal findings from biliary tract, gallbladder, pancreas and liver. However, MRI enterography showed the involvement of CD of multiple ileal loops, liver and spleen enlargement, and a small dilation of portal vein and of veins in the portal of spleen. The small bowel follow-through confirmed the involvement of many loops of jejunum and ileum. Upper GI endoscopy and gastric and duodenal biopsies were negative.

Table 1. Liver function tests in different time periods

Date	SAP (<40-140 IU/L)*	γ GT (15-85 IU/L)	ANA (<1:80)	Antimito-chondrial Abs (<1:40)	anti-M2 (<15 U/ml)
06-04-2004	115	50			
30-09-2009	513	757		1:360	
06-10-2009 [†]	494	731			
30-12-2009	196	241			
13-01-2010	172	218	1:640	1:140	
05-11-2010	229	161			91.1
06-06-2011	246	180			
10-11-2012				1:120	

*Numbers in parentheses are normal values

[†]Date of starting treatment with a dalimumab

Because of the previous intolerance of infliximab, the patient was treated with adalimumab 160mg, then 80mg and finally 40 mg every other week. The response was quite satisfactory. Four months later the titre of serum AMA decreased from 1:360 to 1:160. Anti-M2 antibodies remained positive. In 2011, ursodeoxycholic acid (200mgX2/d) was added, and was well tolerated.

In 2012, an MRCP showed no abnormal findings. His general situation remained satisfactory. The latest (2012) laboratory investigation revealed no anemia with slightly elevated values of liver cholestatic enzymes. The titre of antimitochondrial antibodies further reduced to 1:80. During the 3-year treatment with adalimumab, Reynaud's phenomenon did not appear again. We plan to continue the treatment with both the biologic agent and the ursodeoxycholic acid for the next few years.

Table 1 shows the values of cholestatic enzymes and serum AMA in different time periods before and after the treatment with adalimumab.

Discussion

The described case presents some interesting clinical and epidemiological characteristics. The patient was a man with long-standing CD, having

many members of his family suffering from a variety of autoimmune disorders. During the course of CD i) he developed clinical symptoms of severe hyperthyroidism and as a consequence, he underwent total thyroidectomy the histology of which revealed that hyperthyroidism developed on the ground of Hashimoto thyroiditis, ii) for a long period of time he was suffering from Reynaud's phenomenon, iii) the laboratory investigation revealed that he was also suffering from PBC. In this patient, the treatment with an anti-TNF- α agent (adalimumab) resulted not only in a significant improvement of both CD and perineal disease, but also in a significant reduction in the values of cholestatic enzymes and serum titres of AMA after a 4-month period. Moreover, during the 3-year administration of adalimumab, Reynaud's phenomenon did not appear again. His clinical situation is now quite satisfactory and we plan to continue the administration of adalimumab at least for the next years.

However, many questions should be addressed concerning the diagnosis and clinical outcome in this patient: i) how strong is the diagnosis of PBC?, ii) are indeed the improvement of the titers of both serum AMA and liver enzymes, due to the administration of the biologic agent?, iii) might the appearance of thyroid disease with other autoimmune disorders on the ground of CD be considered as an appearance by chance?

As far as the accuracy of the diagnosis of PBC is concerned, it is widely accepted that this diagnosis could be safely done if at least two of the following three criteria were fulfilled: i.e. serum AMA titers $>1:40$, increased serum alkaline phosphatase levels for more than 6 months, and compatible liver histology in the absence of alternative explanation. However, liver biopsy at the time of diagnosis is currently not indicated except for patients participating in clinical trials and patients requiring accurate staging (6). Generally, high serum titers of AMA are seen in more than 90% of patients with PBC (7), while low-titers are considered to be not specific (8). In our patient, the titers of AMA and the levels of serum cholestatic enzymes were very high, thus establishing the diagnosis of PBC. Today, the increased availability of serological tests have resulted in the establishment of diagnosis of PBC in a very early and almost asymptomatic clinical stage, as it was happened in the reported patient (9).

Other immunological serum findings in patients with PBC include the presence of anti-nuclear (ANA) and anti-smooth muscle antibodies in about 50% of them, a finding that has been linked to a worse prognosis (10). The serum Immunoglobulin M levels are also elevated without being correlated to the AMA levels. In our patient, the serum titers of ANA were very high, while the levels of serum Immunoglobulin M were also above the upper normal limit. ASCA antibodies were positive. These antibodies have been correlated to elevated IgA in patients with PBC suggesting that they might be an indirect sign of an enhanced mucosal immunity (11).

It has been long suggested that serum TNF- α production is related to the severity and prognosis of PBC (12). Moreover, it has been shown that both the levels of serum TNF- α and Transforming Growth Factor- β could be reduced in patients with PBC as a result of the treatment with ursodeoxycholic acid (13). Spadaro et al recently described a patient with PBC and concomitant

rheumatoid arthritis. The patient responded well to the anti-TNF- α treatment with etanercept but not with infliximab. Arthritis, and serum levels of cholestatic liver enzymes, improved and this improvement persisted during a 30-month follow-up period (14).

To the best of our knowledge, our patient is the only case of concurrent PBC, CD and Raynaud's phenomenon described so far, in whom the biologic agent adalimumab was administered. Adalimumab resulted in a great reduction in the serum titers of AMA and cholestatic enzymes and a significant clinical improvement. Although the combined results of recent metaanalysis regarding the role of ursodeoxycholic acid in PBC demonstrated no significant favourable effects concerning mortality, pruritus, fatigue, autoimmune conditions, liver histology, and portal pressure, we decided to add this agent in the therapeutic regime because it seems to improve some biochemical variables, like serum bilirubin and jaundice (15).

Thyroid dysfunction is frequently associated with both PBC and CD sometimes predating the diagnosis of both diseases (16). CREST syndrome is not uncommon in PBC (17). In our patient, Hashimoto thyroiditis and Raynaud's phenomenon also appeared during the course of CD.

Autoimmunity does occur naturally, although the underlying mechanisms remain enigmatic. An imbalance of T cell regulation can initiate or propagate autoimmunity in both inflammatory bowel disease and PBC. In both disorders genetic, environmental and infectious agents have been suggested as triggering or causative factors (18).

It is concluded that the appearance of PBC during the course of CD, although quite rare, is a reality. Extremely rare is also the combination of CD and PBC with autoimmune thyroiditis and Raynaud's phenomenon. It is not clear whether these co-morbidities appeared coincidentally or because they share some common immunopathogenetic elements. The influence of

the treatment of PBC with adalimumab should be further investigated.

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