Successful Etanercept Treatment for Primary Biliary Cirrhosis Associated with Rheumatoid Arthritis

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KEY WORDS: rheumatoid arthritis (RA), primary biliary cirrhosis (PBC), biological therapy, etanercept

IMAJ 2015; 17: 114–116

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Primary biliary cirrhosis (PBC) is a progressive chronic hepatic disease of autoimmune pathogenesis. It is characterized by intrahepatic cholestasis due to intrahepatic bile duct destruction, leading to fibrosis and nodular hepatocellular regeneration. Its exact etiopathogenesis remains unknown [1,2]. The development of the disease is associated with the production of characteristic autoantibodies. The main clinical manifestations of PBC include jaundice, pruritus and xanthelasmata, as well as secondary consequences of malabsorption such as osteoporosis. PBC may be associated with autoimmune manifestations in other organs, such as autoimmune thyroid disease, rheumatoid arthritis (RA), vasculitis, systemic sclerosis, Sjögren's syndrome, and diabetes mellitus [1,2]. The goals of treatment are symptom relief and prevention of further bile duct obstruction and destruction. Pruritus is relieved by cholestyramine, a bile acid sequestrant that prevents the reabsorption of bile acids in the gastrointestinal tract, and by the enzyme inducer phenobarbital. Routine care includes immunosuppressive agents such as corticosteroids, azathioprine, cyclosporine and methotrexate; drugs that may dampen tissue fibrosis including D-penicillamine and colchicine; as well as ursodeoxycholic acid that reduces the concentration of bile acids. As discussed below, there have been attempts to administer biologics to PBC patients. Finally, if cholestasis persists and pruritus becomes unbearable, liver transplant is the only option [1,2].

Rheumatoid arthritis (RA) is also a chronic inflammatory disease involving multiple joints. The development of bone and cartilage erosions may lead to destruction of joint structure and consequent disability [3]. Due to the progressive nature of the disease, early aggressive therapy is of utmost importance [3]. Until the last decade, treatment included the administration of corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and synthetic disease-modifying drugs (DMARDs). In the new millennium, the introduction of biological agents was a real breakthrough. Indeed, considerable clinical improvement and the reduction of radiological progression could be obtained by the administration of anti-tumor necrosis factor (TNF)agents and biologics attacking other targets [3]. We present the case of a woman with coexisting RA and PBC who received anti-TNF therapy.

PATIENT DESCRIPTION

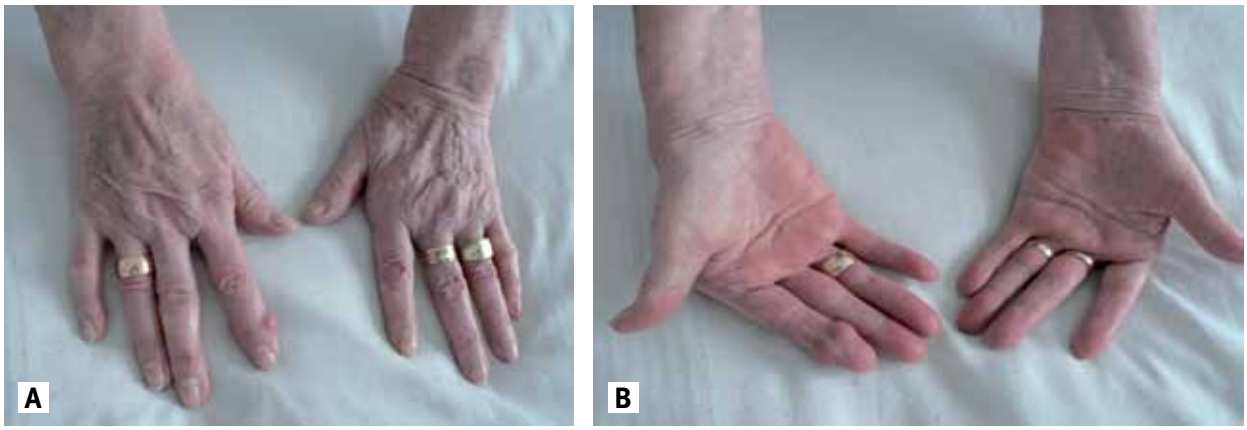
A 67 year old woman had a negative medical history prior to 2005. In that year, elevated hepatic enzymes (alkaline phosphatase, ALP and gamma-glutamyltransferase, GGT), high total bilirubin levels, jaundice and hepatomegaly were observed. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were within the normal range. She underwent cholecystectomy and reoperation was performed twice due to postoperative abscess formation. Despite the surgery, ALP and GGT remained continuously elevated.

In 2006, polyarthritis mostly affecting the small joints of the hand, morning articular stiffness, as well as immunoglobulin (Ig) M rheumatoid factor (RF) positivity lead to the diagnosis of seropositive RA established by a local rheumatologist. DMARD treatment (leflunomide 20 mg/day) was initiated but had to be discontinued due to the sustained elevation of hepatic enzymes. Until 2008 she received methylprednisolone 4 mg/day.

The patient was first admitted to our hospital in Szolnok in August 2012 due to high RA activity. Her main signs and symptoms included sclera jaundice, palpable liver, as well as swollen and tender metacarpophalangeal joints, reduced grip strength, gross interosseus atrophy, and swelling of the right ankle joint.

Laboratory results showed elevated acute-phase reactants: erythrocyte sedimentation rate (ESR) 50 mm/hr and C-reactive protein (CRP) 24.4 mg/L; markedly elevated GGT (702 U/L) and ALP (743 U/L) but only slightly elevated AST (35 U/L) and ALT (41 U/L), and anemia (hemoglobin 117 g/L). Abdominal ultrasonography showed status after cholecystectomy with thickening of intrahepatic bile duct walls but no obstruction of the extrahepatic flow. Since the active RA had to be treated, despite the elevated hepatic enzymes it was decided to admin-

Synovitis of small joints **[A]** is reduced following etanercept treatment **[B]**



ister very low dose methotrexate (MTX) (5 mg/week). Yet, even this very low dose resulted in further increase of GGT (791 U/L) and ALP (762 U/L), and MTX treatment had to be discontinued.

In September 2010, a more detailed hepatological examination was performed. Hepatitis B and C virus serology tests were negative, and immunoserologic tests revealed antinuclear antibody (ANA) positivity (titer > 160). Other autoantibodies (anti-smooth muscle, antimitochondrial, antiparietal cell, antimyeloperoxidase, antiproteinase 3, anticentomere and anticytoplasmic antibodies) were all negative. Based on these observations, PBC was diagnosed and ursodeoxycholic acid therapy was immediately given. Because of increasing RA activity, sulfasalazine was initiated and later combined with chloroquine. However, this combined DMARD therapy had to be stopped due to intense stomach pain, nausea and vomiting. The patient still received continuous low dose methylprednisolone therapy. The concomitant secondary osteoporosis was treated with calcium, vitamin D, and annual infusions of zoledronic acid.

The patient maintained high disease activity (DAS28 5.74) despite corticosteroid treatment, and we therefore considered biological therapy. There was no hepatologic or other contraindications. In December 2010, laboratory tests still showed seropositivity (RF 48 IU/ml, anti-CCP > 500 U/ml), high inflammatory activity (ESR 46 mm/hr, CRP 9.9 mg/L), ANA and anti-dsDNA negativity.

In February 2011, etanercept 50 mg once a week was initiated subcutaneously. As early as within the first 2 weeks the patient noted a considerable amelioration of her arthritic symptoms [Figure 1]. Much to our surprise, after 2 weeks of therapy, hepatic function tests also showed significant improvement (GGT 189 U/L, ALP 341 U/L). This favorable tendency was observed throughout the course of biological therapy (August 2011: ESR 33 mm/hr, CRP 10.3 mg/L, GGT 141 U/L, ALP 356 U/L), but transient ANA positivity (67.1 U/ml) was observed.

During biological therapy the patient's general state was stable. Her arthritic symptoms were relieved to such an extent that in May 2011 the administration of corticosteroids could be terminated. However, in January 2012, at the semiannual pulmonary checkup the chest X-ray indicated an undefined cavernous bean-sized malformation in the right apex of the lung. It was suggested that the treatment be discontinued until a more precise diagnosis could be established. Sputum culture was Koch-negative. In March 2012 a chest computed tomography (CT) depicted pulmonary emphysema and fibrotic scarring, but there was no sign of malignancy or cavity formation. The pulmonologist agreed to the reintroduction of etanercept therapy. Interestingly, increased RA activity and increasing GGT (198 U/L) and ALP (409 U/L) were again observed during the biologic-free period. Thus, in April 2012 etanercept was reintroduced and a few weeks later the patient again reported considerable relief of her arthritic symptoms, and by June 2012 hepatic tests again showed improvement (GGT 164 U/L, ALP 380 U/L). These changes during etanercept treatment and biologic-free periods suggest that anti-TNF therapy exerted significantly beneficial effects on both RA and PBC.

COMMENT

PBC is a chronic autoimmune disease characterized by injury of intrahepatic bile duct epithelia. PBC may be associated with other autoimmune conditions including RA [1-3]. Although 95% of PBC patients are seropositive for antimitochondrial antibodies (AMAs) directed against the inner mitochondrial membrane, pyruvate dehydrogenase and 2-oxoacid enzymes, AMA-negative cases do not differ clinically from those positive to AMA. Furthermore, TNFα and associated genes are involved in the pathogenesis of PBC [2]. There have been case reports on the biological treatment of PBC, but anti-TNF agents have not yet become a part of routine care [1]. Biologics may be primarily used in cases of PBC associated with arthritis, when the underlying rheumatic condition is the main indication for this treatment [1,3].

Our Hungarian colleagues, Laduver et al. [4], presented a similar case in 2009. Spadaro et al. [5] also reported a case of RA-PBC where, due to high disease activity, infliximab was administered initially but had little effect on RA activity or hepatic function test results. Etanercept treatment later resulted in a considerable reduction of activity in both diseases.

In conclusion, anti-TNF biologics appear to be hugely successful in the treatment of arthritis and other chronic inflammatory diseases. As suggested by our case and other case reports, in duly justified cases, the administration of TNFα inhibitors should be extended to the treatment of other immunopathologic diseases, such as PBC.

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