

Primary biliary cirrhosis in a rheumatoid arthritis patient treated with rituximab, a case-based review

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Abstract Primary biliary cirrhosis (PBC) is an autoimmune disease in which intrahepatic bile ducts are targeted by an immune-mediated injury. This disease tends to progress to fibrosis and cirrhosis with hepatic failure. The authors report a case of a 50-year-old rheumatoid arthritis (RA) patient, with erosions and seropositive for rheumatoid factor and anti-citrullinated peptide antibodies, with 18 years disease duration refractory to prednisolone and several disease-modifying antirheumatic drugs, either conventional or biological (adalimumab and etanercept). In April 2007, she started therapy with rituximab (RTX) with good European League Against Rheumatism response achieved 9 months later. In June 2008, she was admitted with intrahepatic cholestasis, steatorrhea, and spontaneous fractures of various ribs. After excluding cholelithiasis, as well as infectious and neoplastic diseases a liver biopsy was performed that was compatible with the diagnosis of PBC. The antinuclear antibodies (1/160) were positive as well as the antimitochondrial antibodies (1/640). Other antibodies were negative such as anti-SSA and anti-SSB. Afterwards, the patient started ursodesoxycholic acid 15 mg kg⁻¹ day⁻¹ with progressive improvement of cholestatic markers. A labial salivary gland biopsy was performed and showed findings compatible with the concomitant diagnosis of

Sjögren's syndrome. Based on this clinical report, a detailed review of the clinical aspects of PBC is presented as well as its association with other immune-mediated inflammatory diseases, particularly, with RA.

Keywords Biologic therapy · Primary biliary cirrhosis · Rheumatoid arthritis · Rituximab

Introduction

Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease characterized by the slow progressive destruction of small bile ducts leading to cholestasis. This chronic non-suppurative cholangitis is immune mediated by CD4+ and CD8+ T cells, anti-mitochondrial antibodies, innate immunity, and IgA transcytosis.

PBC is more frequent in women and it is usually diagnosed by the fourth and fifth decades of life [1–3]. Common disease manifestations are asthenia, chronic pruritis, digestive malabsorption, xanthelasma, and jaundice. However, some studies suggest that in more than half of the patients, the diagnosis is established at an asymptomatic stage [4]. Other disease manifestations include metabolic bone disease, such as osteomalacia and osteopenia, which are likely secondary to the malabsorption. Lab manifestations include moderate to high elevation of alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT), as well as mild transaminases elevation. Bilirubin is usually normal during the early phase of the disease. The presence of anti-mitochondrial antibodies increase the likelihood of the diagnosis, but liver histology is critical to ascertain the diagnosis. Ludwig and Scheuer established four histological stages: portal damage, periportal damage, septal damage, and cirrhosis [5]. Early

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diagnosis of this disease is of outmost relevance since early treatment with ursodeoxycholic acid has proven to be effective in decreasing liver-related mortality as well as the need for liver transplantation [6]. Of note, PBC can be associated with many other autoimmune diseases, such as Sjögren's syndrome (SS), Raynaud syndrome, autoimmune thyroid disease, and systemic sclerosis. In fact, 70% of the PBC patients have sicca syndrome [7–11].

The association of PBC with rheumatoid arthritis (RA) is less clear, although several studies since the 1970s point to a possible association; however, the true prevalence of PBC in RA is not well known, and this may impose several therapeutic and diagnostic challenges as we will demonstrate in this paper [12, 13].

Case report

This case report refers to a 50-year-old patient who was diagnosed with RA in 1990, when she was 32 years old. She presented with 2 years disease duration of symmetric additive polyarthritis involving proximal interphalangeal and metacarpophalangeal joints, wrists, shoulders, knees, ankles, tarsus, and metatarsophalangeal joints, with over 2 h of morning stiffness. She was rheumatoid factor positive ($80 \text{ IU } \mu\text{l}^{-1}$) and had discrete erosions identified in some metacarpophalangeal joints after 2 years of disease duration. She also referred xerostomia, xerophthalmia, and occasional aphthous ulcers. Antinuclear antibodies (including SSA and SSB) were negative, and there was no evidence of keratoconjunctivitis sicca.

She was subsequently treated with several consecutive disease-modifying antirheumatic drugs (DMARDs), starting with sulphasalazine up to 1.5 g day^{-1} that had to be stopped due to nausea and vomiting. She was also treated with prednisolone $5\text{--}10 \text{ mg day}^{-1}$. In 1992, she started gold salts, but had to be interrupted in March 1994 due to aphthous stomatitis. In the meantime, several steroid intra-articular injections were performed (right wrist, second and third metacarpophalangeal joints). In 1995, she started therapy with methotrexate (MTX) up to 7.5 mg week^{-1} , and hydroxychloroquine (HCQ) 400 mg day^{-1} was added subsequently. MTX was also suspended in 1997 due to mucositis. As an alternative to MTX, azathioprine (AZA) was started in a dose up to 100 mg day^{-1} in December 1997. Despite this therapy, she maintained high disease activity (DAS28 of 6.38). She received concomitant treatment with calcium and vitamin D, and as the bone densitometry showed a T-score of -2.26 in the hip and -1.98 in the lumbar spine, she was started on alendronate 70 mg week^{-1} in 2003.

In April 2003, due to sustained high disease activity, she was medicated with adalimumab (ADA) 40 mg

every other week, maintaining AZA, HCQ, and prednisone. As the patient had only a partial response, AZA was replaced by MTX 7.5 mg week^{-1} , in June 2004. However, DAS28 was persistently above 5.2, and she was switched to etanercept in March 2006. Unfortunately, the same pattern of high disease activity persisted under etanercept and she was then proposed for treatment with RTX $1,000 \text{ mg}$ 2 weeks apart, which was started in April 2007. B cell depletion was confirmed. A year later, she was with low disease activity.

In June 2008, she was admitted due to a new onset asthenia, adinamia, and weight loss, as well as slight fever (maximum axillary temperature of 38°C), steatorrhea, and an episode of spontaneous posterolateral right thoracic pain. The physical examination was unremarkable, except for several skin excoriations, and tender palpation of four consecutive right ribs (from fifth to eight). She had elevated GGT (268 IU l^{-1} , seven times upper limit of normal) and ALP (403 IU l^{-1} , four times upper limit of normal). ALP bone isoenzyme was only borderline high ($34.8 \text{ } \mu\text{g l}^{-1}$; $N < 22.5$), despite the fractures. Serum calcium, phosphorus, parathyroid hormone, TSH, and immune electrophoresis were normal. Cultures were negative. By this time, B cells had already repopulated peripheral blood. The chest radiograph showed fractures of four consecutive ribs. Abdominal ultrasound was compatible with hepatic steatosis. The investigation regarding occult neoplasia was negative and the patient was dismissed. At that time, a bone densitometry was repeated and showed a T score of -2.4 in the hip and -2.2 in the lumbar spine. A few months later, the patient was readmitted due to multiple fractures (including a fragility wrist fracture), progressive weight loss (about 20 kg in 6 months), severe steatorrhea, and cholestasis. Reevaluation showed a pseudopolypoid lesion of the duodenum. The biopsy was compatible with ganglioneuroma. However, this finding was not considered to be related with cholestasis, since the endoscopic retrograde cholangiopancreatography was normal and the abdominal ultrasound showed no biliary dilation. The patient had intrahepatic cholestasis, with very high ALP and GGT, mildly elevated levels of TGP and TGO, and elevated IgM. Serum calcium and phosphorus levels were again normal. These clinical and biochemical features were suggestive of PBC, and a liver biopsy was performed which showed findings compatible with this diagnosis, Ludwig's stage 3. Besides, at this time point, antimitochondrial antibodies were positive in high titer ($1/640$), which further supported this hypothesis. She had also positive antinuclear antibodies ($1/160$), with negative anti-double stranded DNA (anti-dsDNA), anti-SSA, and anti-SSB. Ursodiol therapy was started with progressive improvement of the cholestasis markers. A salivary labial

biopsy was performed that showed focal lymphocytic sialadenitis, suggesting SS. A hand ultrasound was performed that confirmed the existence of erosions in several metacarpophalangeal joints and wrists and no synovitis; at that time, the patient was also anti-citrullinated peptide antibodies (ACPA)-positive (178 EU). A couple of months later, the patient was submitted to partial duodenopancreatectomy, and the diagnosis of ganglioneuroma was confirmed.

Reviewing the patient chart, there were previous episodes of elevation of cholestatic markers (ALP and GGT) which were always self-limited, asymptomatic, and interpreted as drug-induced events.

In March 2010, due to disease reactivation, the patient was retreated with RTX, but this time without any clinical significant response. A further switch to abatacept was tried, but currently, RA remains active. CBP manifestations are quiescent.

Discussion

This case report illustrates the association of multiple immune-mediated diseases and the therapeutic challenges which this scenario arises. This patient had a classic, established RA with almost 20 years of disease duration and was exposed to multiple DMARDs, ending with RTX after failing two TNF inhibitors. In fact, there was a clinically significant response (good European League Against Rheumatism response), but when the patient was going to be retreated she was admitted due to severe cholestasis and multiple rib fractures. Chronic cholestasis seemed to explain bone fragility, but the atypical rib fractures forced the work out for an occult neoplasia. Bone metabolic disturbances induced by long-standing RA, chronic corticosteroid treatment, and prolonged exposure to biphosphonates might have contributed for the atypical pattern of bone fragility, initially dominated by multiple rib fractures. In the absence of biliary tree dilation, the investigation had to rely on causes of intrahepatic cholestasis. The clinical presentation and the fact that there were very high levels of ALP and GGT, mildly elevated AST and ALT, and high IgM suggested the diagnosis of PBC, which was confirmed after compatible serology and liver biopsy. After reviewing the patient's chart, there were previous episodes of cholestasis which seemed to be drug-induced; they were always mild to moderate and self-limited. After 1 year of RTX treatment, severe intrahepatic cholestasis surfaced, and interestingly, this event was coincident with B cell repopulation.

Hepatic involvement of most rheumatic diseases is common and usually related with nonspecific findings

(drug-related most of the times). However, more serious hepatic involvement, including vasculitis, nodular regenerative hyperplasia, and primary biliary cirrhosis, have been observed in specific rheumatic diseases, such as RA [14, 15].

Furthermore, ALP elevations in RA are common and rarely related with PBC [16]. In a recent review of 607 patients with diffuse connective tissue diseases, liver dysfunction was observed in 38.2% and PBC was present in 15.9%. This review showed that in scleroderma and SS, PBC was the cause of liver dysfunction in above 70% of the patients, which did not occur in RA where cases of PBC were rare (3 out of 220 patients) [17].

RA is present in about 1% of the population and PBC is even rarer, with an estimated prevalence of 20/100,000 for woman and 2/100,000 for men and the association of both diseases by chance is very unusual [10]. However, there are some reports describing its association in individuals or families [18, 19]. Few studies have suggested an increased prevalence (1.8% and 5.6%) of RA in PBC patients as compared to the prevalence in the general population [4, 20, 21]. In one series of 42 patients with PBC, four presented symptomatic arthritis with rheumatoid factor positivity, and nine had erosions without symptomatic arthritis [22]. In another series, 4 out of 83 patients with PBC presented inflammatory arthritis [23]. In a Japanese review, 3 of the 54 patients with PBC had polyarthritis, without specifying whether or not RA criteria were fulfilled [24]. In a 1980s review of 26 PBC patients, 7 were classified as RA, which seems an overestimation [25]. On the contrary, a recent review of 278 patients with autoimmune hepatitis (some of them overlapping with PBC), 111 had concurrent autoimmune diseases, of which only 5 had RA, according to the ACR 1987 ARA diagnostic criteria [26].

Currently, there is no accurate estimate of PBC prevalence in RA patients but several studies estimated that 10–18% of these patients have antimitochondrial antibodies, which have indeed a high association with PBC. Importantly, most of these patients had associated syndromes, as was the case of our patient. On the other hand, approximately half of the patients with PBC become rheumatoid factor positive during the course of the disease [27–29]. In fact, in an older series, 70% of the PBC patients were rheumatoid factor positive [8]. Serology overlap also happens with ACPA. In fact, according to Koga et al. ACPA are positive in 2.7% of the CPB patients and in 10.5% of the autoimmune hepatitis patients, almost always in association with a clinical presentation compatible with concomitant RA [30]. In another work, Santiago et al. showed that ACPA (third generation) were present in 3.7% of the PBC patients [31].

Despite the low prevalence of PBC in RA patients, auto antibodies overlap and shared genetic risk factors, namely, related with CTLA4 and ICOS SNPs, suggesting the existence of at least some common physiopathological mechanisms [32]. In fact, RTX has been proposed as a treatment option for PBC and curiously overt clinical and laboratorial manifestations of PBC occurred in our patient after B cell repopulation. Another interesting and unexplored field is the disturbance of costimulation that occurs in PBC that might benefit from costimulation modulating therapies such as abatacept [33, 34]. However, the use of abatacept in our patient (introduced for RA treatment) did not influence PBC clinical manifestations.

Key points

- (1) PBC is a rare disease that can appear in association with several other immune-mediated diseases
- (2) PBC's association with RA is unclear despite some reports in the literature suggesting a possible link between both diseases
- (3) In patients with rheumatic diseases, persistent elevation of liver enzymes, mostly with cholestatic pattern, shall raise the suspicion of a possible PBC

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