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Primary biliary cholangitis—cause or association with psoriasis: a case report

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Abstract

Primary biliary cholangitis is a chronic progressive cholestatic granulomatous and destructive inflammatory lesion of small intralobular and septal bile ducts that primarily affects women. The exact etiology of this disease has not yet been elucidated; however, it is believed to be the result of a combination of environmental triggers in genetically predisposed individuals. It can manifest itself simultaneously with, before, or after the onset of psoriasis and other skin autoimmune diseases. Standard treatment is ursodeoxycholic acid. A 65-year-old patient presenting with elevated hepatic laboratory findings that had persisted for several years and normal abdominal ultrasound was additionally diagnosed with primary biliary cholangitis after 2 years on a biological drug for psoriasis. She did not have other symptoms except elevated liver tests. The skin showed a strong response to biological therapy and treatment with ursodeoxycholic acid prompted lowering of liver enzymes. The skin was clear all throughout the treatment. This article emphasizes the importance of additional diagnostic workups in patients with psoriasis and elevated hepatic laboratory findings.

Keywords: primary biliary cholangitis, psoriasis, antimitochondrial antibodies, liver disease

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Introduction

Primary biliary cholangitis (also known as primary biliary cirrhosis, PBC) is a cholestatic liver disease with chronic progression. The main feature of the disease is the destruction of the intrahepatic bile ducts and granulomatous inflammation, which progresses to cirrhosis over time. It is primarily a disease of middle-aged women; only 10% of those affected are male (1). The cause is yet unknown but it is most likely due to a combination of hereditary predisposition and a disturbed immune response to environmental factors. Clinically, the disease can be divided into three forms. The most common is the classic form, in which primary biliary cholangitis is a slowly progressing disease that causes cirrhosis within 10 to 20 years. The second form has a faster course and earlier development of cirrhosis. It occurs as an overlap syndrome with autoimmune hepatitis. The rarest form is seen in 5% to 10% of patients, in whom the course of the disease is extremely rapid. Clinically, there is severe cholestasis with jaundice and the development of cirrhosis in less than 5 years. The basis for making a diagnosis are three characteristic findings. Biochemically, there is an increase in cholestatic enzymes (alkaline phosphatase [AP] and gamma glutamyl transpeptidase [gamma-GT]). Immunologically, there is the presence of antibodies against mitochondria (AMA) and an increase in IgM immunoglobulins. Histologically, there are characteristic changes with gradual deterioration of the bile ducts (ductopenia) and the development of cirrhosis. Liver biopsy is not necessary for a diagnosis, but it helps define the stage of the disease and predict the outcome (2). The goals of treatment and disease management are prevention of end-stage liver disease and improvement of associated symptoms. The standard treatment today is ursodeoxycholic acid, and, in the final stage, liver transplantation (3).

We report the case of a patient with psoriasis and primary biliary cholangitis, who was diagnosed after 2 years of receiving biological therapy for psoriasis. The patient had mildly elevated liver tests for more than 20 years and a normal liver according to an ultrasound exam, therefore, no additional laboratory diagnostics for autoimmune liver diseases were performed upon the introduction of biological therapy. Due to the slightly increased tendency in transaminase values, we decided on additional diagnostics. We confirmed primary biliary cirrhosis and referred the patient to a gastroenterologist. The patient continued her biological therapy for psoriasis. After the diagnosis and taking ursodeoxycholic acid, the skin condition and laboratory findings significantly improved.

Case report

A 65-year-old patient presented to our dermatology clinic in October 2016. For 2 months, she had noticed nonpruritic changes that initially appeared on the front of her left shin. Later, similar minor changes appeared elsewhere: on both shins, the thighs, the back of the hands, and the elbows. She had no changes on her scalp or in her nails. Her family history was positive for psoriasis; her younger son had psoriasis. At that time, she was healthy, without regular therapy. In her clinical status, a small psoriatic plaque stood out on the left shin with a diameter of 2 cm. There were also some smaller papules on the shins, thighs, and backs of the hands. Based on the medical history and clinical picture, the patient was diagnosed with psoriasis. She started local therapy with a combination of calcipotriol and betamethasone plus indifferent topical therapy.

The situation was adequate until the next checkup in July 2019, when her skin condition deteriorated. In regular therapy, she received rosuvastatin 10 mg 1×1 and bisoprolol fumarate 1.25 mg 2×1. The changes became more disturbing and affected her quality of life. In her medical history, she already had slightly elevated bilirubin (20 µmol/l, normal values up to 17 µmol/l) 40 years earlier, whereas the rest of the laboratory values were within normal limits.

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She had similar values for several years, but then 20 years earlier bilirubin decreased to normal values and gamma-GT increased slightly. For this reason, the patient was examined at an infectious disease clinic in 2010. At that time, an elevated gamma-GT of 1.38 µkat/l (normal 0–0.63 µkat/l) was found, and the other results were within normal limits. Serological tests for hepatitis B, C, and HIV were negative. Abdominal ultrasound was advised, which the patient repeated several times over the following years, mainly because of two simple cysts in the left kidney. The liver was always of appropriate size, with a homogeneous structure, without clear focal lesions in the sections examined. In her clinical status, thick typical psoriatic plaques were visible on the shins, 2 to 5 cm in diameter, covered with delicate scales. There were similar changes on the elbows, the thighs, and, to a lesser extent, the torso. The skin was distinctly red (Fig. 1). She scored 25 points on the Dermatology Life Quality Index (DLQI) questionnaire. Laboratory tests were performed, in which elevated gamma-GT of 3.42 and AP of 1.84 µkat/l (normal < 1.74 µkat/l) were found. The patient underwent a chest X-ray, which was normal. Considering the long-term stable state of liver function and the absence of liver damage on ultrasound, acitretin was administered at a dose of 25 mg per day (one capsule), despite the elevated gamma-GT value.

At a follow-up visit in October 2019, despite taking acitretin, the condition of the skin had not improved; in fact, it was even slightly worse. Due to the failure of therapy, which was also difficult to tolerate for the patient, she started with the biological drug guselkumab. The first application was administered in November 2019. This was followed by regular controls and applications of the drug subcutaneously. The condition of the skin improved completely, and in July 2020 there were no more plaques on the skin (body surface area; BSA = 0). In regular therapy, she additionally received acetylsalicylic acid 100 mg 1×1. Liver tests were regularly checked during examinations. In January 2021, AST was within normal limits, whereas ALT (1.81 µkat/l, normal < 0.52 µkat/l) and gamma-GT (4.99 µkat/l) were elevated. In August 2021, AST was also elevated (0.64 µkat/l, normal < 0.52 µkat/l), ALT was 0.63 µkat/l, gamma-GT 5.04 µkat/l, and AP 2.22 µkat/l.

In January 2022, AST (0.58 µkat/l) and ALT (0.53 µkat/l) were only slightly elevated, and gamma-GT (3.96 µkat/l) and AP (2.09 µkat/l) were partially decreased. Due to several years of elevated liver tests, we decided on an extended immunological examination, including antinuclear antibody HEp-2, antibodies against extractable nuclear antigens (anti-ENA), anti-pyruvate dehydrogenase antibodies (anti-PDH), liver panel, and anti-double stranded DNA (anti-dsDNA) tests. The patient also underwent an ultrasound of the abdomen, where, apart from the previously described kidney cysts, there were no abnormalities. She denied pruritus and fatigue. She never had problems with the thyroid gland, and she denied Raynaud's phenomenon and pain below the right part of the rib cage. She had given birth twice; her pregnancies and deliveries were uneventful. On immunological examination, a positive HEp-2 test with a titer of 1:640 and positive nuclear fine speckled antibodies and AMA M2 cytoplasmic antibodies were found (2). Anti-PDH (1) and anti-ENA (rabbit thymus extract; RTE 1) antibodies were also positive. From the liver panel, ANA M2 was positive, with a value of 2. Based on these results, we referred the patient for examination and consultation to a gastroenterologist, where she started treatment with ursodeoxycholic acid. After regular therapy and checkups with a gastroenterologist, the laboratory values of her liver tests improved significantly, and at the last checkup in November 2022, the AST, ALT, gamma-GT, and AP were 0.41 µkat/l, 0.42 µkat/l, 1.12 µkat/l, and 1.97 µkat/l, respectively. TSH and alpha-fetoprotein were within normal limits. A repeated HEp-2 test was positive at a titer of 1:80, whereas nuclear fine speckled antibodies and anti-PDH antibodies and the other findings, including AMA M2, were unchanged. At the time of treatment there were no signs of psoriasis anywhere on the body (Fig. 2).

Discussion and literature review

PBC is a rare chronic autoimmune liver disease. Its incidence is 1.9 to 2.5 patients per 100,000. A possible cause of the onset of the disease could be disturbed immune response to environmental factors in genetically hypersensitive people. The progressive disease leads to the gradual development of cirrhosis (2). The disease is more common in northern Europe and North America, and in the last decade also in southern Europe, especially in central Greece. The incidence is significantly lower in South Korea (4). PBC is a disease of women, usually affecting those older than 50. The female-to-male ratio is 10:1, with 92% patients being women (3). In a study that included 169 Slovenian patients treated at the Ljubljana University Medical Center from 1984 to 2010, there were even more women; namely, 96.5% (2). Regardless of frequency, however, hepatocellular carcinoma (HCC) is significantly more

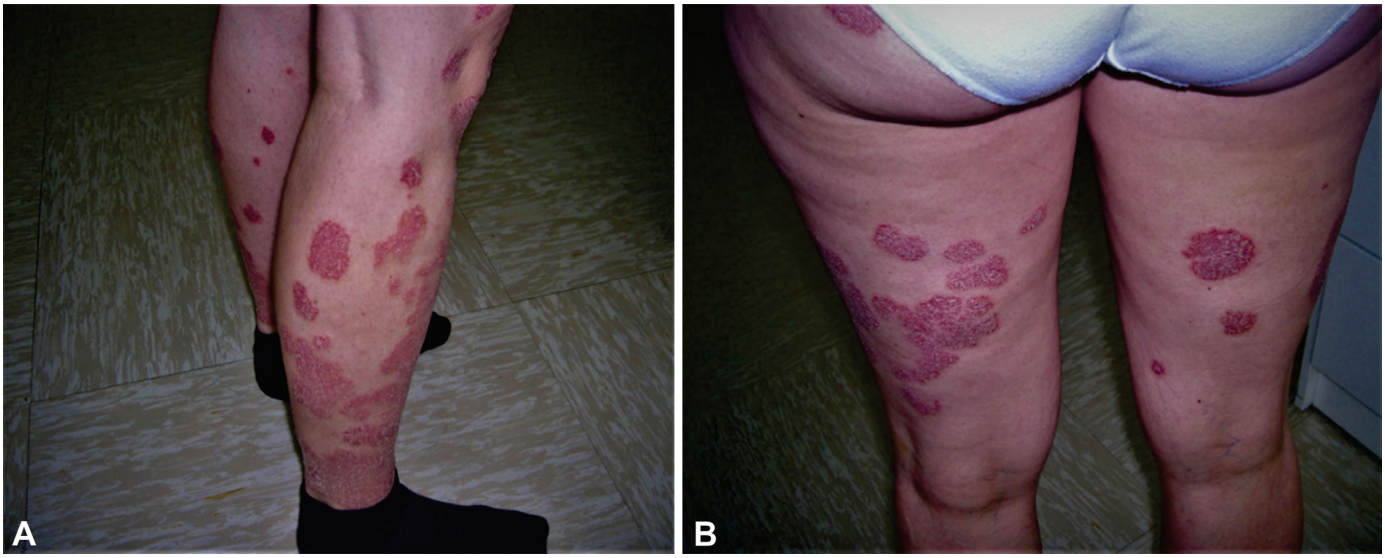

Figure 1 | Skin changes after 3 years of only local therapy for psoriasis.

common in men with PBC. This has been attributed to estrogen-mediated inhibition of cytokines. In addition, the disease is diagnosed and treated earlier in women because the general symptoms of itching and fatigue are expressed earlier. On the other hand, in men, elevated gamma-GT is often attributed to alcohol dependence and probably underestimated (4).

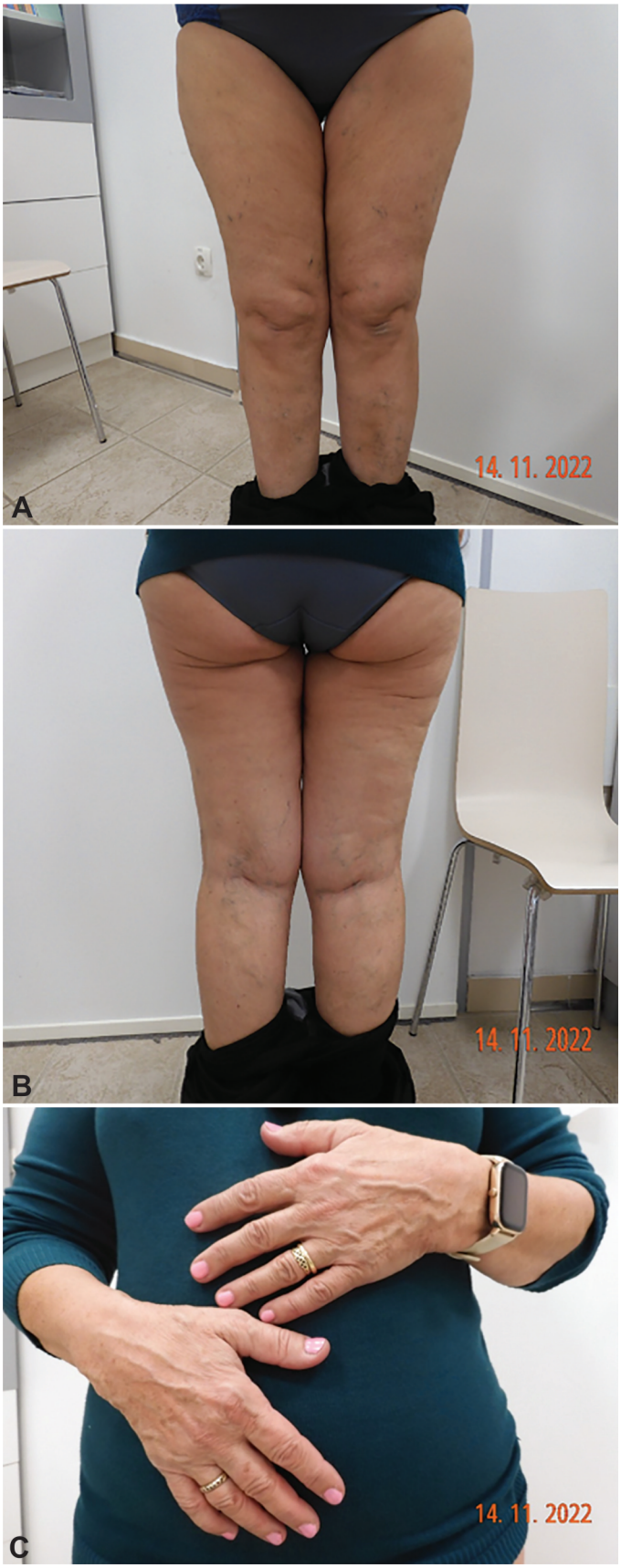

Figure 2 | Skin after 3 years on biological drug therapy for psoriasis.

With our patient, we decided to perform additional laboratory diagnostics because she was a woman and we believed that she did not consume alcohol. The disease should be considered when there are no symptoms of cirrhosis, but there are elevated liver test values. We recorded a gradual increase in liver test values, especially gamma-GT, for several years. For this reason, we decided to perform additional diagnostics, in which we demonstrated positive AMA antibodies, which are one of the main criteria for the diagnosis of PBC.

Patients with PBC more often have additional autoimmune diseases, especially Hashimoto's thyroiditis, Sjögren's syndrome, and Raynaud's syndrome, which are not present in our patient. Hyperlipidemia, which is present in our patient and for which she has been receiving rosuvastatin for the past 3 years, is also common. The following skin diseases are mentioned in connection with PBC: bullous pemphigoid, vitiligo, lichen planus, lichen sclerosus et atrophicus, skin vasculitis, granulomatous diseases, and psoriasis (5). The frequency of psoriasis in patients with PBC ranges from 2% in central Europe to 5% in Norway, and it is slightly higher than in the general population. There are only a few reports available in the literature. Six patients with PBC in connection with plaque psoriasis and three cases of palmoplantar pustular psoriasis are described. PBC was diagnosed in three patients before the appearance of skin changes, and in three patients after they were already known to have psoriasis (6). One case of a patient with psoriasis and subsequently discovered PBC was described in Japan in 1999 (7). As in our patient, an increase in liver test values was observed for several years before deciding on additional laboratory diagnostics and biopsy.

Also interesting is the case of a patient with palmoplantar psoriasis that, in addition to elevated values of liver tests and initial parenchymal liver damage proven by ultrasound, also had negative AMA antibodies at baseline. After 6 months and only topical therapy, the skin condition was excellent, and the liver tests were normal. After 1 year of stable disease, there was clinical and laboratory deterioration, and AMA antibodies became positive. Therapy was started with ursodeoxycholic acid, and after only 2 months there was complete remission in the skin and in blood tests (8).

In the era of treatment of psoriasis with biological drugs, it is possible that patients that may have initially undiagnosed biliary cirrhosis will be unintentionally cured. Specifically, treatment with tumor necrosis factor (TNF) inhibitors has been shown to be successful. Namely, Italian authors have reported successful treatment of psoriatic arthritis and concomitant PBC and primary sclerosing cholangitis. The patient's symptoms of inflammatory arthropathy and cholangiopahty improved significantly after 28 months of treatment with adalimumab and the success of the therapy is believed to be associated with the polymorphism of the TNF gene. Interestingly, the existence of the TNF-alpha gene promoter variants can play both the role of a marker of the severity of the disease and the response to therapy with anti-inflammatory drugs (9). After a transient decrease in liver enzymes in our patient, there was a gradual increase with an otherwise excellent response of the skin lesions to biological therapy. This moderate persistent increase led to an additional diagnosis of liver damage. Although unlikely, it possible that a primary liver lesion was the cause of the first outbreak of psoriasis in our patient at a relatively late age.

In the case of unresponsiveness of PBC to standard therapy, it is therefore feasible to consider replacing biological therapy for psoriasis with anti-TNF after consulting gastroenterologists. Because patients with psoriasis are known to be prone to metabolic

syndrome with hepatic steatosis, abstinence from alcohol is especially important because it often leads to a significant improvement in skin changes.

Conclusions

We would like to emphasize that in patients with autoimmune skin diseases and concurrent hepatopathy without a history of alcohol abuse, physicians should develop a broad differential diagnosis. Sudden exacerbations of skin diseases or the first outbreak of psoriasis in older people should lead physicians to think about additional diagnostic workups for liver diseases.

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