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Case Report

Amelioration of limited mouth opening after treatment of primary biliary cholangitis: A case report

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ABSTRACT

Primary biliary cholangitis is a slow-progressing autoimmune disease of the liver characterized by the presence of portal inflammation and immune-mediated destruction of the intrahepatic bile ducts. Herein, we report a case of temporomandibular joint disorder that concurred with primary biliary cholangitis. A 54-year-old woman presented to us with severe pain on the left side of the temporomandibular joint and difficulty in mouth opening. We used pharmacotherapy, occlusal sprint, and arthrocentesis for the treatment; however, there was no improvement. Magnetic resonance imaging revealed malposition of the articular disk on the left side of the joint and joint effusion. Thus, we performed arthroscopic surgery under general anesthesia. Postoperatively, she developed impaired liver function and itchiness of the skin. A liver biopsy was performed by a hepatologist, and a diagnosis of primary biliary cholangitis was made, as suspected. The temporomandibular joint pain and trismus persisted postoperatively; however, these symptoms improved after primary biliary cholangitis therapy. Thus, we suggest a relationship between temporomandibular joint disorder and primary biliary cholangitis from this disease trajectory and suspect that interleukin-17 may play an important role in the pathogenesis of temporomandibular joint disorder.

1. Introduction

Primary biliary cholangitis (PBC) is an autoimmune disease characterized by chronic and progressive cholestasis. PBC often affects some members of the same family, and it appears that the first-degree relatives of PBC patients are at an increased risk of disease development. The major complication associated with this disease is the destruction of small-sized biliary ducts, which can lead to cholangitis. The disease most commonly affects women aged 35–45 years. Prolonged liver inflammation can cause scarring, leading to cholangitis [1–5].

In such cases, liver biopsies reveal signs of chronic nonsuppurative inflammation, cholangitis, and fibrosis. Ludwig and Scheuer described the following four stages: portal damage, periportal damage, septal damage, and cholangitis. In PBC, ursodeoxycholic acid has been proven to be effective in preventing liver deterioration, and in decreasing liver-related mortality and the need for transplantation. PBC is characterized by the presence of several disease-specific autoantibodies in the serum [6]. The serologic hallmark of PBC in 95%–98% of the patients is the presence of M2 anti-mitochondrial autoantibodies (AMAs) directed against the E2 subunit of the pyruvate dehydrogenase multi-enzyme complex located in the inner membrane of mitochondria. AMA positivity appears to be indicative of future PBC development. Although in some cases, the clinical course may proceed at a faster rate, PBC generally progresses slowly. The diagnostic criteria of PBC include the following: (1) biochemical evidence of cholestasis, such as elevated alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GTP) levels,

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(2) the presence of disease-specific AMAs, and (3) histological features of PBC. Additionally, elevation of immunoglobulin M (IgM) levels is a common observation. While elevated serum interleukin (IL) −2, −4, and −10 levels have been reported in patients with PBC, the most significant elevation has been noted in interferon (IFN)-γ and IL-5 levels when compared to normal controls [7].

The most common early clinical manifestations are pruritus, asthenia, or jaundice; however, most patients remain asymptomatic. PBC may be associated with arthralgia, but its association with polyarthritis and synovitis is rare. Further, PBC is often associated with other non-liver autoimmune diseases, especially primary Sjogren's syndrome. It has been suggested that PBC and rheumatoid arthritis (RA) coexist in 1.8–5.5% of PBC patients; however, there is little data supporting this association [8].

Recently, IL-17 has been identified as a key inflammatory cytokine involved in a number of autoimmune diseases, including RA, experimental autoimmune encephalitis (EAE), and colitis. Because IL-17 levels in the peripheral blood of PBC patients have been found to be elevated and to correlate with clinical stages, they may be indices that could be used to clinically monitor PBC [9].

Herein, we report a case of a patient with temporomandibular joint (TMJ) disorder exhibiting such an association. This patient presented with severe TMJ disorder without RA. There have been no reports of TMJ disease complicated by PBC without RA. Furthermore, we discuss the therapeutic management of such patients and investigate IL-17 messenger RNA (m-RNA) levels in synovial tissues.

2. Material and methods

2.1. RNA extraction and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis

Synovial fibroblasts were obtained from a fractured patient, and informed consent was obtained before treatment using a procedure approved by the ethics committee of Kyushu Dental College. The synovial fibroblast cells were then harvested, centrifuged at 4 °C, and stored at −80 °C. mRNA was extracted from cell pellets using a Cica Geneus RNA Prep Kit (KANTO CHEMICAL, Tokyo, Japan).

Real-time RT-PCR primers were designed by using Primer Express 3.0 software (Applied Biosystems, Foster City, CA, USA). We performed the detection with an AriaMx Real-Time PCR System (Agilent Technologies). Total cDNA abundance between samples was normalized using the GAPDH gene expression.

The primers used for real-time RT-PCR were as follows: GAPDH, forward 5′-ATG GAA ATC CCA TCA CCA TCT T-3′ and reverse 5′-CGC CCC ACT TGA TTT TGG-3′; IL-17, forward 5′-AGG CCA TAG TGA AGG CAG GAA TCA-3′ and reverse 5′-ATT CCA AGG TGA GGT GGA TCG GTT-3′.

2.2. Statistical analysis

Statistical analyses were carried out using JMP® software, version 10.0.2 (SAS Institute Inc., Cary, NC, USA). Data were expressed as the mean ± SD of three individual experiments and analyzed by one-way analysis of variance (ANOVA) followed by a suitable post hoc test (Tukey's) for multiple comparisons. $P < 0.05$ was considered statistically significant.

3. Case report

The present case involved a 54-year-old woman who had severe pain on the left side of the TMJ and had a limited mouth interincisal opening (MIO) for the past 6 months. On clinical examination, we did not observe any facial swelling or asymmetry, and there was no tenderness of the masticatory muscles on palpation. Maxillary molars were missing bilaterally, and she was wearing an ill-fitted denture. Her MIO was 16 mm; this interfered with her daily activities, including chewing, talking, yawing, sneezing, and sleeping. The pain was constant at a level of 6 on a 10-point scale. She could recall no precipitant event and denied trauma to the jaw. Furthermore, she was negative for rheumatoid factor, and her radiographs did not show any abnormality. Therefore, we decided on an initial clinical diagnosis of temporomandibular joint disease (TMD) III b. We fabricated a new denture and initiated treatment using pharmacotherapy (non-steroidal anti-inflammatory drugs), physical therapy, habit control, occlusal splint use, and arthrocentesis; however, the symptoms persisted. Magnetic resonance imaging revealed joint effusion and malposition of the articular disk on the left mandibular condyle; thus, we performed arthroscopic surgery under general anesthesia. However, postoperatively, she developed impaired liver function and itchiness of the skin. A hepatologist examined her and suspected PBC.

The success of arthroscopic surgery has drastically changed the surgical intervention aimed at the treatment of TMJ internal derangement and arthrosis [10]. Thus, we performed arthroscopic surgery on the TMJ as a priority to improve her quality of life. The arthroscope was inserted into the superior joint space, and inflammation and fibrillation were observed on the left side of the upper joint compartment (Fig. 1). However, most joint surfaces were found to be intact on the right side. Postoperatively, the jaw manipulation improved the MIO to 40 mm. Furthermore, synovial fluid lavage samples from both the symptomatic TMJ and an asymptomatic control were analyzed along with an examination of arthroscopic morphology. At a 1-month postoperative follow-up, the patient could open her mouth to 40 mm. However, the visual analog score of TMJ pain was still 4. Two months postoperatively, trismus reoccurred, and the mouth opening reduced to 25 mm. Three months postoperatively, ursodeoxycholic acid treatment was initiated for PBC. Following this, the trismus improved in accordance with the improvement in liver function. On the last postoperative follow-up, the mouth opening was 40 mm and patient had no TMJ pain. There was no recurrence for 2 years after PBC treatment.

4. Result

Biochemical and immunological examination results showed high γ-GTP, ALP, AMA, anti-mitochondrial-M2 (AMA2) antibody, and IgM levels in the peripheral blood sample. AMA2, a specific antibody for PBC, and high IgM levels were detected only in the synovia from the affected side of the TMJ (Table 1). In our presented case, using immunohistochemistry, we also detected the presence of IL-17-positive

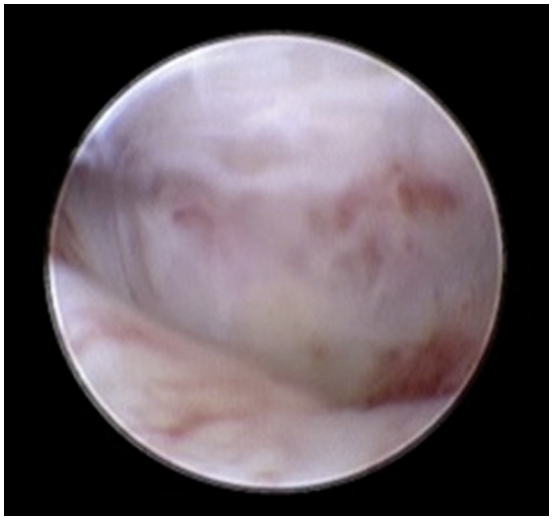

Fig. 1. Arthroscopic view of the upper joint compartment of left side TMJ. The arthroscope shows inflammation and fibrillation were observed on the only left side of the upper joint compartment.

Table 1
Biochemical Characteristics of a primary biliary cholangitis (PBC) PatientAST, aspartate-aminotransferase; ALT, alanine-aminotransferase; GGT, gamma-glutamyl-transferase; ALP, alkaline phosphatase; T-BIL, total bilirubin; D-BIL, direct bilirubin; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; AMA, anti-mitochondrial M antibody; AMA2A, anti-mitochondrial M2 antibody; ACA, anti-centromere antibody; ANA, anti-nuclear antibody; anti-SSAab, anti-Sjögren's-syndrome-related antigen A; anti-SSBab, anti-Sjögren's-syndrome-related antigen B; RF, rheumatoid factor; HCVab, hepatitis C virus antibody; Hbsag, hepatitis B virus antigen.

	Blood	Synovial fluid	
		Left side	Right side
AST (U/L)	31		
ALT (U/L)	40		
GGT (U/L)	339		
ALP (U/L)	582		
T-BIL (mg/dl)	0.5		
D-BIL (mg/dl)	0.1		
IgG (mg/dl)	1023		
IgA (mg/dl)	371	105	14
IgM (mg/dl)	297	79	8
AMA (U/ml)	40	–	–
AM2A (U/ml)	71	50	–
ACA (U/ml)	20	–	–
ANA (U/ml)	80	–	–
anti-SSAab(U/ml)	–	–	–
anti-SSBab(U/ml)	–	–	–
RF (U/ml)	–	< 3	< 3
HCVab (COI)	0.04		
HBsag (IU/ml)	0.01		

Aspartate-aminotransferase(AST), alanine-aminotransferase (ALT), gamma-glutamil-transferase (GGT), alkaline phosphatase (ALP), total bilirubin(T-BIL), direct bilirubin (D-BIL), immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), anti-mitochondrial M antibody (AMA), anti-mitochondrial M2 antibody (AM2A), anti-centromere antibody (ACA), anti-nuclear antibody (ANA), anti-Sjögren's-syndrome-related antigen A (anti-SSAab), anti-Sjögren's-syndrome-related antigen B (anti-SSBab), rheumatoid factor (RF), hepatitis C virus antibody (HCVab), hepatitis B virus antigen.

cells in the liver with PBC (Fig. 2). Additionally, using RT-PCR, we observed that IL-17 m-RNA levels were elevated in the synovial tissues of the affected side of the TMJ when compared to those of the control TMD model in which cultured synovial fibroblasts from normal fractured patients were stimulated using IL-1 and high-molecular-weight hyaluronic acid (Fig. 3).

5. Discussion

IL-17-producing CD4 (+) helper T (Th17) cells that have been identified as one of the major pathogenic Th cell populations is the basis of the development of many autoimmune diseases, and IL-23 is known

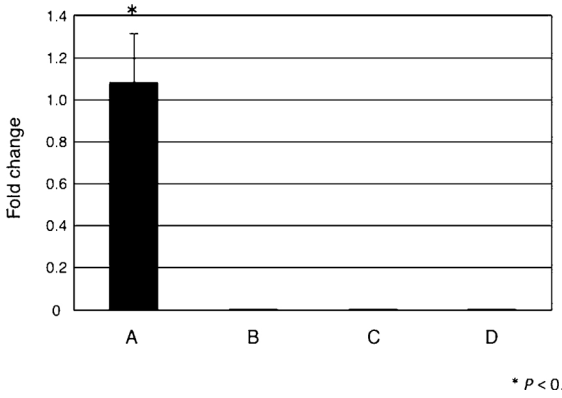

Fig. 3. Real-time reverse transcriptase–polymerase chain reaction for interleukin-17 (IL-17).
Sample A is synovial tissue (present case). Sample B is monolayer of synovial fibroblast from human TMJ. Sample C is monolayer of synovial fibroblast from human TMJ treated with IL-1β (10 ng/ml) for 6 h. Sample D is monolayer of synovial fibroblast from human TMJ treated with IL-1β (10 ng/ml) and HMW-HA (500 ng/ml) for 6 h.

to enhance and stabilize them. [11]. The discovery of the cytokine identity of the IL-17 family and the discovery that IL-23 mediates the proliferation of IL-17 producing T cells led to the discovery of a new subset of Th cells called Th17 cells. Like Th1 and Th2 cells, Th17 cells require specific cytokines and transcription factors for their differentiation and play an important role in inducing inflammatory processes [12]. The immediate body protective response to foreign pathogens and the immune response need to be controlled to avoid tissue destruction mediated by them in the form of chronic inflammation. The main T-cell subsets involved in inflammatory reactions are Th1 and Th17 cells. There are evidences that Th17 cells can be induced by CD4 + T cells, and the effect of cytokines such as IL-6, IL-21, IL-23, and TGF-β in the development of Th17 cells has been clearly mentioned [13]. Accumulating evidence suggests an important role of IL-17 in the pathogenesis of several inflammatory diseases, including PBC.

PBC remains an enigmatic autoimmune liver disease, much like several other autoimmune diseases, characterized by the presence of AMAs and damage to small bile ducts, particularly in women [1–5]. Cytokines and tissue microenvironments play an important role in the regulation and propagation of inflammatory responses [14]. Currently, IL-17 and Th17 have been identified as important key inflammatory cytokines involved in PBC as well as in a number of autoimmune diseases, including RA, EAE, and colitis [15–17].

IL-17-positive infiltrating mononuclear cells were reported to be present mainly at the interface of inflamed portal tracts in cases of PBC and chronic viral hepatitis C, and also accumulated around the damaged interlobular bile ducts including ducts affected by chronic non-

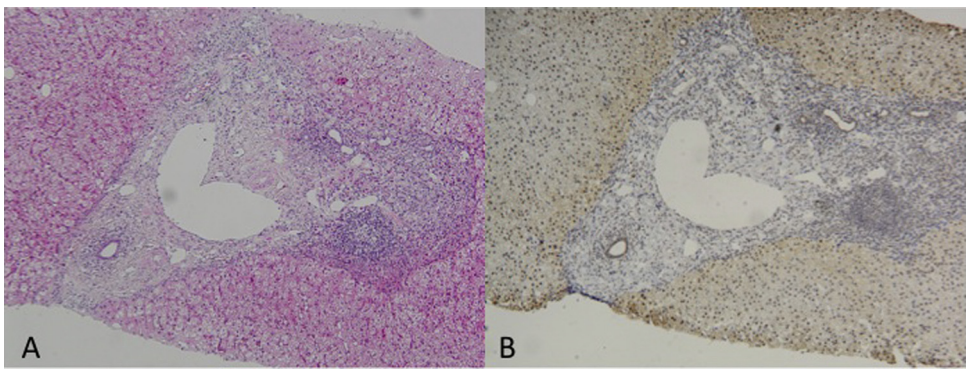

Fig. 2. Liver immunohistochemical staining of interleukin-17 (IL-17) in patients with primary biliary cholangitis (PBC). A: Hematoxylin–eosin staining, B: IL-17 magnification: ×125.

suppurative destructive cholangitis in PBC [18].

Several clinical studies have indicated a pivotal role of IL-17 in the pathogenesis of RA. IL-17 induces secretion of IL-6 by rheumatoid synoviocytes, and both tumor necrosis factor-α and IFN-α augment IL-17 activity [19]. Further, IL-17 has been shown to be an inducer of synovial inflammation and cartilage degradation, an inhibitor of chondrocyte proliferation, and a stimulator of NO and osteoclastogenic cytokine (e.g., IL-1 and IL-6) production. Recently, it has been reported that IL-17, rather than IL-12 or IFN-α, is critical to the onset of autoimmune arthritis. Additionally, IL-17 has been involved in the induction of proinflammatory cytokines, chemokines, and matrix metalloproteinases, and it has been directly involved in diseases characterized by bone and/or cartilage destruction [19–21]. Thus, we suggest that chronic inflammation in the TMJ and IL-17 cytokines are possibly related and conducive to react with each other.

Some papers allow us to possibly attribute a role to IL-17 in the osteoarthritis–TMJ pathophysiology [22]. For the case presented herein, we performed radical TMD treatment. The patient healed temporarily; however, TMD immediately recurred. Mitochondrial antibodies specific for PBC were detected in the synovial fluid of the affected side. Additionally, high levels of IL-17 were detected in the synovial membrane resected during the surgery. There have been no reports of TMD complicated by PBC without RA. In the present case, we could not detect the RA marker. We suggest that Th17 cells produced due to PBC might exacerbate local inflammation. This report is the first to discuss PBC and a chronic, localized disease of the TMJ. Our case presentation and research data suggest that Th17 cells may be induced and transported to the TMJ and maintained there by the IL-23 produced due to chronic condylar inflammation. On the basis of these results, we propose that TMD might worsen in the presence of a Th17-related disease, including PBC. In fact, TMD, which did not show any improvement with conventional treatment, improved after the treatment for PBC in our patient. Further research and case accumulation for TMD and Th17-related diseases are warranted.

Disclosures

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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