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Primary Sclerosing Cholangitis In A Patient With Ankylosing Spondylitis And Ulcerative Colitis Successfully Treated With Adalimumab – A Five Year Follow-Up. Case Report

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***Abstract*— We report a five year follow-up of primary sclerosing cholangitis (PSC) in a 29-year-old man with ankylosing spondylitis (AS) and ulcerative colitis (UC). According to our knowledge, this is the first case report of such coexistence.**

Endoscopic retrograde cholangiopancreatography (ERCP) and the magnetic resonance cholangiopancreatography (MRCP) confirmed PSC. The sphincterotomy was performed and stent to the common bile duct was inserted. Because of the high activity of AS, treatment with adalimumab was started.

***Index Terms*—primary sclerosing cholangitis, ankylosing spondylitis, ulcerative colitis, adalimumab.**

I. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown aetiology. PSC is an irreversible process, frequently seen in young males with inflammatory bowel disease (IBD). The diagnosis of PSC is based on typical cholangiographic abnormalities seen on magnetic resonance cholangiopancreatography (MRCP) or endoscopic reverse cholangiopancreatography (ERCP)[1, 2].Ankylosing spondylitis (AS) is a chronic seronegative spondyloarthritis with sacroilitis and spondylitis [3]. Approximately 90% of AS patients express the HLA-B27 genotype, underlying a strong genetic association. Symptoms of AS have usually been established as long as 8–10 years prior to X-ray-evident changes occurring on a plain film X-ray, which means that there can be a delay in diagnosis of up to 10 years [3]. The literature suggests that approximately 30% of patients with AS may have inflammatory lesions of the colonic mucosa revealed with colonoscopy [4]. Colonic inflammation on histology was found in 54% of AS patients. Ulcerative colitis is an inflammatory bowel disease (IBD) that characteristically involves the large bowel. Findings on colonoscopy with histological changes of colon biopsy confirm a diagnosis [4]. Numerous studies have demonstrated that there is an association between AS and UC [4].

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II. The Case

We report here a 29-year-old man who was admitted to our department in November 2008 complaining of inflammatory back pain over the last 9 years and a 10 month history of bloody and mucous diarrhoea. Physical examination showed increased thoracic kyphosis, decreased lumbar lordosis, restricted motion of thoracic, lumbar and cervical spine (Otto test: 0 cm, Schöber test: 1 cm, chest expansion: 2 cm, lateral lumbar flexion 4 cm, cervical rotation: 10 degree), BASDAI (Bath Ankylosing Spondylitis Disease Activity Index – BASDAI) of 8 and a visual analogue scale (VAS) pain of 80 mm.

Laboratory tests revealed: increased erythrocyte sedimentation rate (ESR) 33 mm/h, elevated C-reactive protein (CRP) 62.7 mg/l, negative rheumatoid factor, positive HLA-B27 antigen, increased level of immunoglobulin A (IgA) 4.4 g/l, interleukin 23 (IL-23) level of 0 pg/ml, interleukin 6 (IL-6) level of 62.99 pg/ml, negative antinuclear antibodies (ANA), negative anti-neutrophil cytoplasmic antibodies (ANCA), normal levels of alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGTP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Stool tests for Clostridium difficile, Salmonella, Shigella and Yersinia were negative.

X-ray examination of sacroiliac joints demonstrated bilateral partial ankylosis of sacroiliac joints (3- rg stage of radiographic sacroilitis), X-ray examination of thoracic and lumbar spine presented syndesmophytes. The diagnosis of AS was based on the New York criteria (X-ray 3rg stage bilateral sacroilitis and restricted anterior and lateral flexion of lumbar spine) [5]. The patient also met the ASAS criteria for axial spondyloarthritis (inflammatory back pain in a young men persisting over 3 months, X-ray sacroilitis, positive HLA B27) [6].

Colonoscopy revealed widespread universally thickened mucosal folds with no visible vascular pattern throughout the entire colon. Histology showed lymphoid cell infiltration of the epithelium surface with formation of the lymphoid follicles and crypt abscesses confirming the diagnosis of UC [4].

The treatment with intravenous methylprednisolone (in a dose of 500 mg for 3 days) was introduced and continued

with oral methylprednisolone (MP) (8 mg/day), sulfasalazin (2 x 1000 mg/day), and azathioprine (2 x 50 mg/day), with vitamin D and calcium supplementation.In January 2009, the patient developed acute abdominal pain. Laboratory tests revealed: increased CRP level (474 mg/l), leukocytosis (19.6 tys/µl), and increased amylase activity in both serum (474 IU/l) and urine (6067 IU/l). He was diagnosed with acute pancreatitis and azathioprine treatment was discontinued.

In March 2009, the patient was complaining of increased intensity of diarrhoea (up to 10 stools per day). Laboratory tests revealed: increased CRP level (159.8 mg/l), leukocytosis (13.8 tys/µl), and increased activity of AP (221 U/l). The flare of UC was diagnosed. He received intravenous methylprednisolone (in a dose of 500 mg for 3 days), and continued with oral MP (8 mg/day), mesalazine (3 x 1000 mg/day) and azathioprine (3 x 50 mg/day), with improvement.After 2 weeks, the next episode of acute abdominal pain occurred. Laboratory tests revealed: increased CRP level (42.1 mg/l), leukocytosis (19.3 tys/µl), abnormal liver function (ALT: 124 IU/L) and cholestasis (AP: 395 IU/L, GGTP: 188 IU/L); amylases were normal and anti-smooth muscle antibodies (ASMA) were negative. Endoscopic retrograde cholangiopancreatography (ERCP) showed narrowing of the distal part of the common bile duct with retrograde dilatation of bile ducts suspected for PSC. The sphincterotomy was performed and stent (8.5 F with a length of 70 mm) was inserted. The treatment with ursodeoxycholic acid (UDCA) (2 x 250 mg/day was introduced and MP and azathioprine discontinued.

As the patient was complaining of increased AS activity (BASDAI: 10, VAS: 100 mm), treatment with adalimumab (40 mg subcutaneously every 2 weeks) was started in October 2010. After that, a significant improvement in clinical (BADAI: 4.0; VAS: 40 mm) and laboratory (CRP: 3.7 mg/l) measures was observed. In October 2011, the patient developed multiplace osteoporotic vertebral fractures (thoracic vertebrae 8 and 10, lumbar vertebrae 1, 2, 3 and 4) and was put on oral alendronate sodium (10 mg/week).

In June 2012, laboratory tests revealed normal liver function (AST: 15 U/l, ALT: 22 U/l, AP: 66 U/L, GGTP: 26 U/l). The magnetic resonance cholangiopancreatography (MRCP) showed intrahepatic bile ducts with irregular contours and segmental narrowing, without the dominant stenosis, confirming PSC (Figs. 1, 2). Following the recommendations by recent American Association for the Study of Liver Diseases (AASLD) guidelines, treatment with UDCA was discontinued [1].The patient remains on treatment with adalimumab, a low dose of MP and alendronate sodium with vitamin D and calcium supplementation; his liver function is normal. During the adalimumab treatment, no exacerbation of AS, UC or PSC was observed.

III. DISCUSSION

Primary sclerosing cholangitis may coexist with various autoimmune conditions. In the available literature, we did not find data on the coexistence of PSC with AS and UC. According to our knowledge, this is the first case report of such coexistence. In the presented case, AS was diagnosed first followed by UC and finally PSC.

Age at onset of PSC follows a bimodal pattern, with a peak at 15-25 years and a less pronounced one at 55-65 years, often in male patients [1, 2]. Also, AS starts in the second and third decade of life, often in males [3]. Our patient was a young man. The diagnosis of AS is believed to have been delayed by about 9 years, as the symptoms of inflammatory back pain were present for this long. This supposition is confirmed by the presence of the third stage X-ray sacroilitis at the time of diagnosis. The diagnosis of PSC was based on a combination of clinical features and cholestatic biochemical profile, with typical cholangiographic abnormalities (ERCP, MRCP). ERCP and MRCP are the gold standards in the diagnosis of PSC; on this basis, the diagnosis was made in the current case [1, 2].There are data indicating that approximately 30% of patients with AS have inflammatory lesions of the colon mucosa in colonoscopy [4]. Histological changes characteristic for inflammation of the colon intestine mucosa were found in 54% of AS patients. In most cases, these changes were of a chronic type. Numerous studies have demonstrated that there is an association between AS and UC. The coexistence of AS and UC has been previously described [4], and the same was observed in our case.

About 2.5-11.8% of patients with UC develop PSC as an extraintestinal manifestation. On the other hand, in up to 73% of patients with PSC, IBD occurs [1, 2, 4, 7, 8]. We can consider the same association in our case.

There are data showing that the interleukin-23/T-helper-17 (IL-23/Th17) pathway plays a key role in the pathogenesis of AS and IBD [9, 10]. We previously published a study presenting a lack of correlation between serum interleukin-23 (IL-23) and AS activity assessed by BASDAI, CRP and ESR [11]. There are also data to confirm the correlation of serum IL-6 and disease activity in AS and UC [12, 13]. In the present case, we reported a similar situation, where serum IL-23 was 0 pg/ml while AS and UC were active and BASDAI, the concentration of CRP, serum interleukin-6 (IL-6) and ESR levels were elevated. In the available literature, we did not find any data concerning the role of serum IL-6 and IL-23 in PSC.The coexistence of PSC, AS and UC may be associated with genetic predisposition. In patients with AS and UC, the HLA-B27 antigen is present [3, 4]. Moreover, in patients with inflammatory bowel diseases associated with arthritis, an association of HLA-DRB1*0103, B*35 and B*27 has been shown [4, 14]. Genes that encode factors that function in the interleukin- 23 pathway have been associated with a number of chronic inflammatory diseases, notably psoriasis and ankylosing spondylitis [9]. In contrast, PSC is more common in patients with HLA-B8 and DR3 [15, 16]. Distinct genetic associations indicate that the colitis associated with PSC is pathophysiologically distinct from UC that is not associated with PSC.

As a result of the active intestinal symptoms of UC, the treatment of AS with non-steroidal anti-inflammatory drugs was contraindicated. Oral glucocorticosteroids and azathioprine are effective in UC but not considered effective for AS [3, 17]. The treatment with TNF blockers is effective in AS and UC [17, 18, 19]. We used adalimumab for the treatment of active AS; this drug is also used in UC treatment.There are data to suggest that short term (2-3

weeks) stenting of bile duct was effective management in PSC and this management was performed in our case [20, 21]. Several agents have been assessed for the treatment in PSC but almost all were found ineffective. There is some controversy surrounding the effectiveness of UDCA treatment in PSC [21, 22]. In our case, low doses of MP and UDCA were initially used, and then MP treatment was continued whilst UDCA was discontinued with no exacerbation of PSC.

In the available literature, there are no data about the use of TNF blockers in patients with PSC. On the other hand, the use of TNF blockers in PSC is not contraindicated. Since in our case the adalimumab treatment was started, we did not observe the exacerbation of AS, UC and PSC. To the best of our knowledge, this is the first case of PSC treated with adalimumab which was effective and resulted in insignificant side effects.

IV. CONFLICT OF INTEREST

All authors indicate that there is no any potential conflict of interest that might constitute an embarrassment to any of the authors.

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