The Journal of Rheumatology 2021;48:11
doi:10.3899/jrheum.201552
First Release September 15 2021

The Journal of Rheumatology

Case Report

IgG4-related Disease in a Patient With Ankylosing Spondylitis: Clues to Common Immunopathogenesis

To the Editor:

Ankylosing spondylitis (AS) is an inflammatory arthritis predominantly affecting the spine. IgG4-related disease (IgG4RD) rarely affects patients with other rheumatic diseases. We describe a report of IgG4RD developing in a patient with AS.

Approval for the publication of this case report was granted by our institutional research ethics board (08.0126). Patient consent was obtained.

The patient is a 59-year-old male with AS. He started infliximab (IFX) in 2003, achieving remission. In November 2019, he developed abdominal pain. Investigation revealed intrahepatic biliary duct dilatation on abdominal ultrasound. Blood tests showed alanine transaminase (ALT) 734 U/L (range 7–40), alkaline phosphatase 248 U/L (range 40–150), aspartate transaminase (AST) 657 U/L (range 15–46), gamma-glutamyl transferase 672 U/L (range 15–73), and amylase 152 U/L (range 25–125). A urinalysis revealed no abnormalities and serum creatinine was within normal limits. Abdominal magnetic resonance imaging revealed a hilar mass encasing the proximal to mid common bile duct, thereby creating an obstruction. The presumptive diagnosis was cholangiocarcinoma. IFX was discontinued.

A computed tomography scan of the abdomen was ordered for staging (Figure 1A) and was reported as a "long stricture of the common hepatic and proximal common bile ducts with periductal soft tissue thickening. Pancreatic inflammatory changes with diffuse soft tissue thickening, peripancreatic inflammatory changes likely representing IgG4-related hepatobiliary disease. Extensive bilateral renal parenchymal scarring (low density areas) was thought to reflect renal involvement."

IgG4 levels were found to be elevated (2.430 g/L, range 0.039–0.864) with normal malignancy biomarkers (carcinoembryonic antigen, serum alpha-fetoprotein, and cancer antigens [CA19-9]). A biopsy was not obtained due to the risk associated with the location, and the clinical presentation fulfilled the classification criteria for IgG4RD with a score of 35 points (elevated serum IgG4: 6 points; pancreas/hepatobiliary involvement: 19 points; and bilateral renal cortex low density: 10 points).[1] The patient was started on prednisone (40 mg daily) and subsequently showed improvement in both symptoms and imaging (Figure 1B). Repeat liver function tests 6 months later showed ALT 23 U/L, alkaline phosphatase 63 U/L, and total bilirubin 8 μmol/L. His IgG4 levels also decreased to 1.020 g/L.

Our case describes a patient with AS developing IgG4RD. IgG4RD occurred more than 16 years after the diagnosis of AS and could suggest that the coexistence of IgG4RD and AS is simply a coincidence. However, age-matched disease onset has not always been observed in chronic rheumatic diseases in which immune response has continuously been activated. For instance, Tarhan, *et al* reported a case of SLE coexisting with AS in a female patient.[2] Her inflammatory back pain emerged at 55 years of age, 8 years after the diagnosis of SLE. Although it is very uncommon to start exhibiting AS symptoms at the age of 55 years in females, images showed bilateral grade 2 sacroiliitis with extensive bone marrow edema. These findings suggest that SLE with prolonged immune activation may have set the stage for AS at a different timepoint. Therefore, it is conceivable that chronic immune activation caused by AS predisposed our patient to IgG4RD.

Immunologically, there are multiple overlaps between AS and IgG4RD. First, it is known that T cell–mediated B cell differentiation and class switching play pivotal roles in the onset and

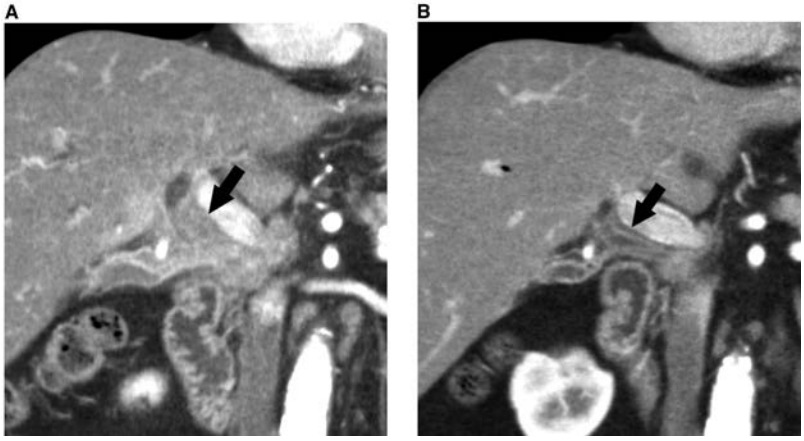

Figure 1. Coronal CT images through the porta hepatis following intravenous contrast administration. (A) Soft tissue infiltration (arrow) encases and obstructs the common hepatic duct, causing intrahepatic biliary dilation. (B) Following treatment, 51 days later, the soft tissue infiltration has almost completely resolved with mild residual mural thickening of the common hepatic duct (arrow) and improvement in intrahepatic biliary dilation. CT: computed tomography.

development of IgG4RD. During this process, T follicular helper (Tfh) cells produce interleukin (IL)-21 to efficiently activate B cells. A previous study showed that patients with IgG4RD have a higher proportion of circulating T cells expressing IL-21, which could facilitate the production of IgG4 through the activation of B cells.[3] Interestingly, in AS there is an elevation of Tfh cells expressing IL-21.[4] In AS, higher serum levels of IL-21 are positively correlated with the levels of immunoglobulin,[5] suggesting that in AS, increased levels of IL-21 could drive the activation of B cells, resulting in the production of antibodies including IgG4.

Beyond IL-21, the serum level of IL-33 is elevated in both AS and IgG4RD.[6] Plasmacytoid dendritic cells producing IL-33 are increased in IgG4RD and assist the differentiation and class switching of B cells through IL-33–mediated activation of Th2 and group 2 innate lymphoid cells producing IL-4 and IL-13. Moreover, a distinct CD4+ cytotoxic T cell subset exists in IgG4RD.[7] This T cell subset, which is also common in other rheumatic diseases, might be an immunological link between IgG4RD and AS.

Factors other than T cell and B cell activation could be implicated in the development of IgG4-RD in AS. A large genome-wide association study in Japanese IgG4RD patients revealed *HLA-DRB1* and *FCGR2B* to be susceptibility loci for IgG4RD.[8] These 2 genes are also associated with AS.[9] While our case is the first report of AS concomitant with IgG4RD, to our knowledge, we previously reported a suggestive overlap that may indicate this occurs more commonly than suspected.[10]

This is a unique case showing the development of IgG4RD in a patient with preexisting AS. Fortunately, the patient was diagnosed with IgG4RD before treatment for the initial presumptive diagnosis of malignancy. It is a cautionary note to be alert to atypical causes of liver function test abnormalities in patients with AS.

Sophie Wojcik[1,2], MD, FRCPC
Robert D. Inman[1,2,3,4], MD, FRCPC
Akihiro Nakamura[1,2,4,5], MD
[1]Toronto Western Hospital, and Spondylitis Program, University Health Network;
[2]Department of Medicine, University of Toronto;
[3]Department of Immunology, University of Toronto;
[4]Division of Genetics and Development, Krembil Research Institute;
[5]Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada.

Address correspondence to Dr. S. Wojcik, Jewish General Hospital, Department of Rheumatology, 3755 Ch de la Cote-Ste-Catherine, Montreal, QC H3T 1E2, Canada. Email: sophie.wojcik@mcgill.ca.
Or Dr. R.D. Inman, Toronto Western Hospital, University Health Network, 399 Bathurst Street, 1E423, Toronto, ON M5T 2S8, Canada. Email: robert.inman@uhn.on.ca.

ACKNOWLEDGMENT

We would like to thank Dr. Anthony Hanbidge, radiologist affiliated with the University of Toronto, Department of Medicine, and the University Health Network in Toronto, Ontario, for his contribution to this paper.

REFERENCES

1. Wallace ZS, Naden RP, Chari S, Choi HK, Della-Torre E, Dicaire JF, et al; Members of the ACR/EULAR IgG4-RD Classification Criteria Working Group. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IGG4-related disease. Ann Rheum Dis 2020;79:77-87.
2. Tarhan F, Argın M, Can G, Özmen M, Keser G. Coexistence of systemic lupus erythematosus and ankylosing spondylitis: another case report and review of the literature. Eur J Rheumatol 2014;1:39-43.
3. Chen Y, Lin W, Yang H, Wang M, Zhang P, Feng R, et al. Aberrant expansion and function of follicular helper T cell subsets in IgG4-related disease. Arthritis Rheumatol 2018;70:1853-65.
4. Xiao F, Zhang HY, Liu YJ, Zhao D, Shan YX, Jiang YF. Higher frequency of peripheral blood interleukin 21 positive follicular helper T cells in patients with ankylosing spondylitis. J Rheumatol 2013;40:2029-37.
5. Wu S, Yang T, Pan F, Xia G, Hu Y, Liu L, et al. Increased frequency of circulating follicular helper T cells in patients with ankylosing spondylitis. Mod Rheumatol 2015;25:110-5.
6. Watanabe T, Yamashita K, Arai Y, Minaga K, Kamata K, Nagai T, et al. Chronic fibro-inflammatory responses in autoimmune pancreatitis depend on IFN-alpha and IL-33 produced by plasmacytoid dendritic cells. J Immunol 2017;198:3886-96.
7. Mattoo H, Stone JH, Pillai S. Clonally expanded cytotoxic CD4(+) T cells and the pathogenesis of IgG4-related disease. Autoimmunity 2017;50:19-24.
8. Terao C, Ota M, Iwasaki T, Shiokawa M, Kawaguchi S, Kuriyama K, et al. Igg4-related disease in the Japanese population: a genome-wide association study [abstract]. Lancet Rheumatol 2019;1:PE14-22.
9. Reveille JD, Zhou X, Lee M, Weisman MH, Yi L, Gensler LS, et al. HLA class I and II alleles in susceptibility to ankylosing spondylitis. Ann Rheum Dis 2019;78:66-73.
10. LeBlanc CM, Inman RD, Dent P, Smith C, Babyn P, Laxer RM. Retroperitoneal fibrosis: an extraarticular manifestation of ankylosing spondylitis. Arthritis Rheum 2002;47:210-4.