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Takayasu's Arteritis Associated with Crohn's Disease and Autoimmune Thyroiditis: An Unusual Association with Diagnostic and Therapeutic Difficulties

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Abstract **Case Report**

The coexistence of Crohn's disease (CD) and Takayasu's disease (TD) does not seem to be accidental and does not seem to modify the natural course of the 2 pathologies. The granulomatous character of the inflammatory infiltrate of the vascular wall appears to be the result of the pro-inflammatory effect of several cytokines, such as TNF and the IL-6, -8, -12 and -18 common to both entities. The literature reports more than 40 cases of Takayasu's disease associated with Crohn's disease. However, the association of these two pathologies with autoimmune thyroiditis has never been described before in the literature. In a case hospitalized in the gastroenterology department of the Mohammed VI University Hospital in Marrakech, of a woman with autoimmune thyroiditis treated by total thyroidectomy and hormone replacement therapy, Crohn's disease and Takayasu's disease for which she was treated by antiTNF treatment and the evolution was marked by a good clinical response.

Keywords: Crohn's disease (CD), Takayasu's disease (TD), inflammatory infiltrate, antiTNF treatment.

INTRODUCTION

Takayasu's disease (TD) is a chronic inflammatory vasculitis of the large vessels of unknown etiology. It affects essentially the aorta and its main branches, the coronary and pulmonary arteries. It is a granulomatous panarteritis characterized by the appearance of arterial strictures, more rarely by the formation of aneurysm, also called the disease of women without a pulse. Crohn's disease (CD) is a recurring, autoimmune disease characterized by transmural inflammation that can affect any segment of the gastrointestinal tract. The prevalence of Crohn's disease in developing countries and southern climates like Morocco is considered to be lower, compared to countries in Western Europe [1, 2]. Although an association between Takayasu's disease and Crohn's disease in the same patient is rare and has been described in the literature only rarely, there may be a common pathophysiologic link that may induce chronic inflammation. However, the association of these two diseases with autoimmune thyroiditis has never been described before, to our knowledge. In this regard, we report the case of a patient with autoimmune thyroid disease associated with Crohn's disease, who subsequently presented with TM, and we will provide a review of the literature.

CASE PRESENTATION

GR A 42-year-old female with a type I diabetes evolving since the age of 20, revealed by an inaugural ketosis, treated by insulin therapy, she had no notable family history and she had consulted at the age of 32 for inconstant abdominal pain, associated with recurrent episodes of watery diarrhea, according to laboratory tests, inflammatory markers (SV and CRP) were still high. However, no specific treatment has been instituted. At the age of 38, the patient presented to the emergency for abdominal pain, with mucous-bloody diarrhea, the physical examination objected to a blood pressure of 120/60 mmhg, a heart rate of 74 beats per minute, a temperature of 38.4 °C. The initial laboratory assessment (Table 1) revealed microcytic hypochromic anemia at 10 g / dl (normal 12-16g / dl), an increase in C-reactive protein at 120 mg / L (normal 0-5 mg / L) and sedimentation rate at 90 mm / h and hypoalbuminemia at 25 g / L (normal 32-45 g / L). The

abdominal ultrasound revealed a regular circumferential rectal thickening, with infiltration of adjacent fat. Colonoscopy (Figure 1) revealed an erythematous colonic mucosa, with aphthoid ulcers, irregular ulcers of varying size and morphology, as well as pseudo-polypoid lesions. Histological study showed on ileal and recto-colic biopsies an inflammatory lympho-plasma cell infiltrate, mixed with a few tuberculoid follicles without caseous necrosis, with a few cryptic abscesses, which confirms the diagnosis of Crohn's disease. Treatment with oral corticosteroid therapy and Azathioprine was started. The clinical and biological progress under treatment was good, but the patient stopped treatment 6 months later due to lack of money.

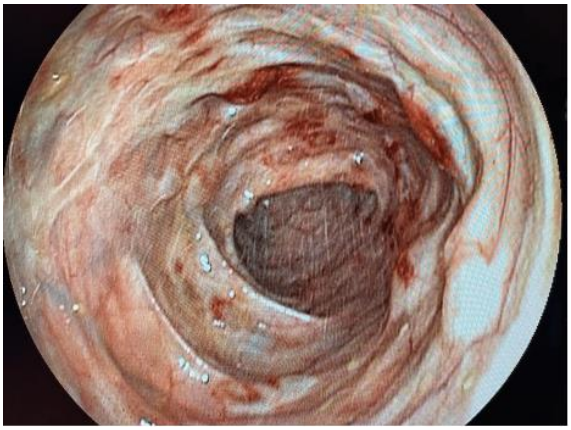

Figure 1: Erythematous colonic mucosa, aphthoid ulcers, and pseudopolypoid lesions in colonoscopy

At the age of 40, the patient returned to our intension, for a compressive nodular thyroid goiter, there was an increase in TSH, and a low T3 and T4, an immunological assessment had detected a high concentration of anti-thyroglobulin antibodies (AC anti-TBG), the diagnosis of an autoimmune thyroid disease was made, thus surgical treatment consisting of thyroidectomy, as well as hormone replacement therapy were initiated. One year later, while still on treatment, she reported the emission of stool and gas from the vagina, a pelvic magnetic resonance imaging (MRI) showed a rectovaginal fistula. She also complained of exertional dyspnea, intermittent claudication of both upper limbs and right carotidodynia. The physical examination noted an asymmetry of the cervical pulses with a weaker pulse on the right, auscultation revealed a bilateral carotid murmur and at the level of the abdominal aorta. Biologically, there was an inflammatory biological syndrome with a sedimentation rate of 70 mm the first hour and a high C reactive protein at 40 mg / l. The arterial doppler ultrasound of the cervical arterial axes showed a diffuse thickening to 11mm at the level of the primary carotid arteries (Figure 2), with a stenosis of the right carotid artery of 40%, and of the left carotid artery of 48%, without hemodynamic repercussions downstream; in the abdominal aorta, she objected to a tight stenosis of the abdominal aorta, with a very accelerated flow at this level, responsible for a hemodynamic impact on the arteries of the lower limbs; Abdominal CT angiography (Figure 4) had shown extensive stenosis of the infra-renal abdominal aorta which becomes completely occluded 2.8cm from the iliac bifurcation, with repermeabilization by a collateral branch preventing the superior mesenteric artery. This patient was diagnosed with Takayasu disease associated with Crohn's disease and the treatment with anti-TNF (Infliximab) has been started. The evolution was marked by a good clinical response at 6 months of follow-up.

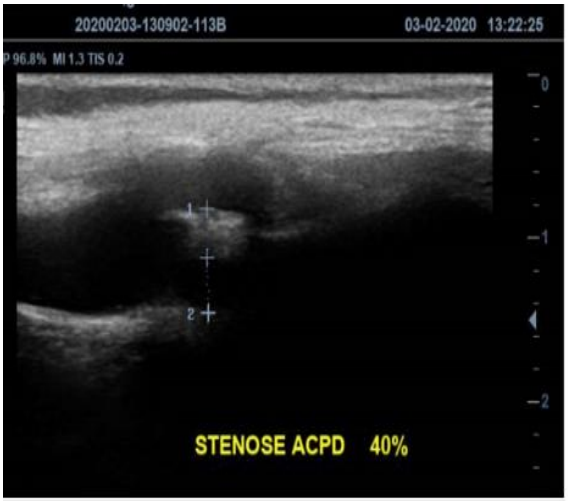

Figure 2: Arterial doppler ultrasound of the Right common carotid artery with stenosis of 40%

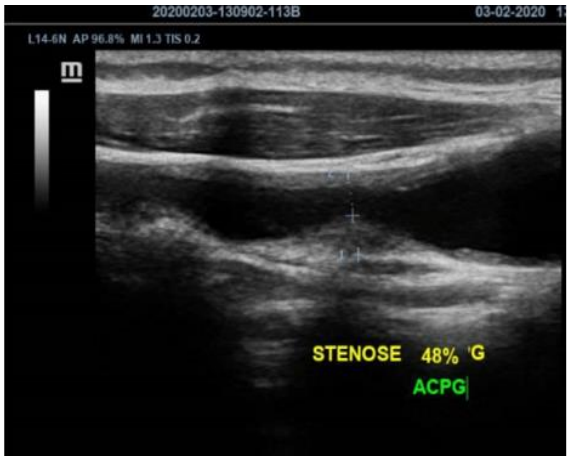

Figure 3: Arterial doppler ultrasound of the of the Left common carotid artery with stenosis of 48%

DISCUSSION

Takayasu's disease (TD) is an infrequent large vessel arteritis whose origin remains unknown. Its association with other systemic diseases including Crohn's disease (CD) is exceptional. The literature reports to date, about forty observations relating to the association between Takayasu disease and Crohn's disease [3, 4]. In 80% of cases, the diagnosis of TD is simultaneous or subsequent to that of CD.

Takayasu disease (TD) is a rare idiopathic, inflammatory and granulomatous vasculitis affecting the large arteries, including the aorta and its major branches [5], it is the most commonly reported vasculitis with inflammatory disease of intestine (IBD). Crohn's disease (CD) is a chronic inflammatory disease of the bowel with extra-intestinal manifestations. The prevalence of CD in patients with Takayasu's disease is rare and is thought to be 0.05% to 0.2% [6].

The data show that in most patients with both TD and CD, the diagnosis of CD always preceded the diagnosis of TM, consistent with our patient's case [6-8]. Soloway et al. in 1970 reported the first case of TD with IBD [8]. In Turkey, a study was conducted in 52 patients with Takayasu's disease, showed symptomatic IBD was present in 5.8% of patients and preceded the diagnosis of TD by 9, 30 and 60 months. TD was diagnosed due to the presence of arterial hypertension associated with persistent weight loss and elevation of acute phase reagents despite immunosuppressive therapy. However, none of the patients or controls tested positive for P-ANCA or ASCA [9].

There are nearly 100 case reports in the literature describing the association of these two diseases. Indeed, five different studies have demonstrated the relationship between CD and TD in these studies, the frequency of IBD in patients with TD has been reported between 6.3% and 9.3% [10-12]. TD and CD have many characteristics in common, including age of onset, female predominance, granulomatous inflammation, and the benefits of anti-TNF therapy [9]. The mechanism of this association has not yet been elucidated. CD is a chronic inflammatory disease in the terminal ileum and colon that can cause excess antigens due to tissue damage and / or bacterial translocation. The cross-reaction of antibodies against other organs is believed to be responsible for digestive and extra-digestive symptoms, such as joint, skin and eye symptoms. Therefore, an immune response to aortic antigens can trigger vascular pathology. Despite differences in their demographic and clinical characteristics, the two pathologies share several similarities. Both occur preferentially in young female subjects. The presence of an inflammatory granulomatous infiltrate is common to both entities [13]. The granulomatous nature of the inflammatory infiltrate of the vascular wall appears to be the result of the pro-inflammatory effect of several cytokines, such as TNF alpha and IL6, 8, 12 and 18 common to both entities. From an immunological standpoint, a mechanism essentially including TH1-type lymphocytes is implicated in the pathophysiology of the two pathologies. Moreover, they could be based on a common genetic ground (HLA B5 group) [14]. Some cases appear when patients are receiving corticosteroid therapy or generally low-dose immunosuppressive therapy for their Crohn's disease. One case describes the occurrence of Takayasu's arteritis in a patient treated with Infliximab for Crohn's disease, attributed to a possibly insufficient dose of Infliximab to treat arteritis [15].

A study [16] identified 132 cases of vasculitis induced by anti-TNF agents and in particular infliximab commonly used in the treatment of Crohn's disease. However, in this study the vasculitis was leukocytoclastic in 72% of cases and there were no reported cases of Takayasu's disease. The granulomatous inflammation seen in both Takayasu disease and Crohn's disease is sensitive to TNF and typically improves after treatment with anti-TNF agents. The role of treatment for Crohn's disease in the onset of Takayasu's disease therefore seems to be excluded [17]. Regarding autoimmune thyroiditis, the association of autoimmune thyroiditis and Crohn's disease has been reported in the literature but rare. However, many studies report the association of autoimmune diseases, including autoimmune thyroiditis, Graves disease or Takayasu's arteritis, in patients with Crohn's disease [18, 19]. Additionally, the association of Crohn's disease with autoimmune thyroiditis has been attributed to a functional single-nucleotide polymorphism in intracellular tyrosine phosphatase (PTPN22), confirming the risk of other autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis and systemic lupus erythematosus [20]. Finally, most patients who present with a combination of different chronic conditions, as illustrated in this case, need prompt treatment in order to improve the prognosis of their illnesses. Indeed, thyroid dysfunction can affect the progression of Crohn's disease [20].

The prognosis for this combination of diseases looks good. Previously, an 81% remission rate in MT and IBD was reported. Glucocorticoids and other immunosuppressive drugs (azathioprine or methotrexate) are the most widely used [17].

CONCLUSIONS

Despite differences in their demographic and clinical characteristics, CD and TD share several pathophysiological, immunological and genetic similarities. The combination of these two diseases is rare, which poses the problem of systematic screening of one entity in the presence of the other. We should consider Takayasu's disease as a complication when cardiovascular symptoms, such as hypertension or the discovery of a murmur, appear in patients with CD.

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