CLINICAL COMMUNICATION

Takayasu’s arteritis associated with Crohn’s disease

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Received 27 November 2013; accepted 13 January 2014
Available online 21 February 2014

Introduction

Takayasu’s arteritis (TA), is a chronic idiopathic granulomatous inflammation of the aorta and its major branches, which leads to wall thickening, fibrosis, stenosis, occlusion and often aneurysm formation, affecting mainly Asian women of child-bearing age.

Crohn’s disease (CD) is a chronic granulomatous inflammatory disease characterized by transmural inflammation and can involve any part of the gastrointestinal tract, resulting in significant complications such as abscesses, fistulas, and strictures. CD is often associated with extraintestinal complications, with manifestations in various organs such as the skin, eyes, joints, and cardiovascular system.

Several case reports have noted TA and CD in the same patient, though such coexistence is rare, there could be a common pathophysiological link between these two diseases to induce chronic inflammation. Herein, we report a rare case of secondary hypertension, a complex case of TA associated with CD with bad response to conventional immunosuppressive and biologic treatment, after total proctocolectomy with end ileostomy.

Case report

We report the case of a 25-year-old Caucasian female with CD and family history of her father having Ulcerative Colitis. She was first diagnosed of inflammatory bowel disease (IBD) at the age of 8, based on bloody stool, ferropenic anemia and endoscopic findings, which revealed macroscopic involvement from rectum to sigma, with redness and multiple small erosions. The biopsy findings were compatible with the diagnosis of severe active ulcerative colitis. She remained with a good clinical response on oral and topical salicylates, and only one severe flare-up episode required hospitalization and systemic corticosteroid treatment.

In 2006, at the age of 19, the disease activity persisted high, with anemia and inflammatory markers elevated, erythrocyte sedimentation rate (ESR) 45mm/h [range: 3–20] and C-reactive protein (CRP) 8.2mg/dL [range: 0–0.8]. The colonoscopy showed edema of the mucosa, erythematous appearance, petechiae, superficial ulcerations and loss of haustrae, moreover cytomegalovirus was undetectable. She started treatment with azathioprine (2.5mg/kg/day) and oral prednisone (60mg/day), but she developed gastrointestinal intolerance to azathioprine. We tried treatment with 6-mercaptopurine (25 mg/every 48h) but she also developed gastrointestinal intolerance. We considered trying administration of anti-TNF-α treatment for continuous inflammatory disease and the patient received infliximab (IFX) infusions at weeks 0, 2 and 6 according to the conventional procedure (5mg/kg), and following,
every 8 weeks. Although a partial clinical response was obtained, biological (CRP 4.96 mg/dL, ESR 78 mm/h, fibrinogen 558 mg/dL [range: 170–437]) and endoscopic activity persisted despite IFX treatment. One year after she required corticosteroids again and became steroid-dependent with lack of response to IFX. At that point, we suggested her go on surgery, though the patient refused. The patient started a program of leucocytapheresis (10 sessions in 2 months), IFX infusions every 4 weeks and also oral and topical salicylates in high doses. Six months later, there was no improvement in the biological markers. Thus, anti-TNF therapy was changed from IFX to adalimumab (40 mg/week). However, acute phase reactants relapsed (CRP 10.7 mg/dL, ESR 81 mm/h, fibrinogen 522 mg/dL) and endoscopic activity worsened (rectum stricture, pseudopolyps, touch friability and macroulcers in colon).

Finally, in 2010, she underwent subtotal colectomy with end ileostomy because of a lack of response to medical treatment. Since the surgery, she had been on rectal mesalazine, without any symptoms. The histology found a granulomatous colitis with aphthoid ulcers, patchy lesional distribution with sharply delineated areas of disease surrounded by normal mucosa, and transmural inflammatory involvement with a reactive lymphadenitis response. Our patient was re-evaluated and finally was diagnosed to CD according to histologic criteria. Acute phase reactants remained high. Short time later, we proposed her proctectomy and a permanent stoma as a better alternative, but the patient rejected.

At the age of 25 years old, 18 months after surgery, the patient consulted in emergency department because of headache and severe hypertension. She did not complain of upper limb sorness or fatigue. On examination, a systolic ejection murmur was heard radiating mid abdomen, and the right humeral and radial pulses were markedly weaker. Blood pressure in the left upper limb was 200/120 mmHg, while on the right side could not be measured. Laboratory results showed elevated inflammatory markers, ESR 99 mm/h, CRP 3.3 mg/dL, white blood cell count 12,000/μL [range: 4500–10,800], red blood cell count 4.0 million/μL [range: 4.2–5.4], hemoglobin 11.2 g/dL [range: 12–16], hematocrit 35.3% [range: 37–47], platelet count 302,000/μL [range: 150,000–400,000] and total protein 8.8 g/dL [range: 6.6–8.7]. Liver enzymes indices and coagulation were normal. Renal test function showed an elevation of creatinin 1.14 mg/dL [range: 0.1–0.95].

Ultrasonography revealed homogeneous wall thickening of right common carotid, subclavian and axillar artery, with a suspected significant stenosis of both renal arteries. All consistent with long-standing hypertension of probable renal origin.

Ophthalmologic examination did not reveal any signs of retinopathy. Echocardiography only showed a moderated tricuspid incompetence, which could estimate a pulmonary pressure of 35 mmHg.

Subsequent computed tomography angiography scanning (CTA) revealed thickening of the wall at the juxtarenal aorta, with extension into the proximal renal arteries and the celiac trunk, in addition, the right subclavian artery was markedly narrowed. CTA findings were confirmed by magnetic resonance (MR) (Fig. 1A, B). There was no evidence of stenosis in pulmonary arteries or aneurysms in the aorta. Together, the diagnosis of type IV TA was established (according to Numano Classification).

Due to the severe activity of the TA, treatment with prednisone (60 mg/day) and methotrexate (10 mg/week, SC injection) were started. Decreases in CRP and ESR were achieved, thus, maintenance therapy was continued.

Currently, at the time of writing, she does not have any active disease on prednisone 20 mg/day, which is tapering, and methotrexate (10 mg/week). Six months later, her inflammatory markers remain low, ESR 10 mm/h, CRP 0.1 mg/dL, meanwhile, due to her medically refractory renovascular hypertension, percutaneous transluminal renal angioplasty (PTRA) was scheduled and performed 2 months later (Fig. 2A, B), with significant improvement in renal function and hypertension control one month after the procedure.

Discussion

The case here presented shows the association of a difficult to treat CD and a TA. The patient was first diagnosed with IBD in 1995, followed by a diagnosis of ulcerative colitis 6 years later, although finally confirmed to be affected with CD based on histologic findings 1 year ago (A1 L2 B1 Montreal Classification), a change of diagnosis that has been reported in some studies.1-3 She was diagnosed of a TA recently, despite being treated with different anti-TNF biological therapies in the past. This unexpected coexistence could have influenced to the responsiveness to medical therapy and the atypical presentation of CD in this patient, which have been reported in the literature.4

TA is known to be a type of idiopathic, inflammatory, granulomatous vasculitis mainly involving the aorta and its main branches. The prevalence of this rare disease is higher in young Asian woman,5 with 150 new cases occurring each year in Japan, in comparison, in Western countries its incidence has risen, having 1–3 new cases per year per million population in United States and Europe.6 The 15-year survival rate is more than 80%.7 Early diagnosis and treatment are very important for patients with TA to prevent vascular complications.

The chance for the two diseases to occur in the same patient is estimated to be 1 per 10 billion persons.8 The first case of CD associated with TA was described by Gateau et al. in 1970.9 Since then, many cases of this unusual association have been reported sporadically in the literature, Kusunoki et al.10 reviewed and listed 37 cases of CD and TA reported in the literature, founding that the age of onset of TA symptoms was simultaneous or later than that of CD in most of them. The long term prognosis of each disease in patients with both is unknown. Reny et al.11 reported that CD was present in 9% of a group of 44 TA patients, and pointed out that in these cases tended to be younger the age at diagnosis, and also tended to have systemic symptoms more frequently than those with TA alone (features such as Raynaud phenomenon, weight loss, fever, arthralgias, myalgias). Moreover, they noted that the distribution of vascular lesions in patients with both diseases were more frequent with the involvement of the supra aortic arches, instead of aorta, supraaortic trunk, pulmonary arteries, femoral, renal, mesenteric, coronary, vertebral arteries, more common of patients with TA alone.
The pathogenesis of both diseases share a common feature of autoimmune origin, highly suggestive of cell-mediated autoimmunity, where includes predominantly CD4 lymphocytes, dendritic cells and common inflammation mediators (Interferon-γ, TNF-α, cytokines, oxidative and growth factors), resulting in a granulomatous inflammation, \(^\text{12,13}\) highlighted in the histologic findings of the present case. The immunologic mechanism proposed is that TA and CD are primarily Th1 dominant conditions, and the cytokines involved in this response may play an important role in the pathogenesis of both diseases; \(^\text{14,15}\) in this regard, some studies highlighted the use of anti-TNF alpha, as infliximab, or more recently, anti-interleukin-6 receptor (IL-6R) antibody, tocilizumab, \(^\text{16}\) might show beneficial therapeutic effects in both diseases, \(^\text{17,18}\) which had been effectively used, even in a significant number of steroid-refractory TA. \(^\text{16,19,20}\)

Some reports have demonstrated the development of vasculitis as an adverse effect of infliximab, \(^\text{21}\) or the detection and extent of the vasculitis according to the degree of inflammation in IBD, \(^\text{22}\) although no relation with TA has been found, it is worth consideration.

Various HLA haplotypes (HLA-A24, B52, Dw12 and DR2) are seen in patients with both Crohn’s disease and TA. A genetic link has not been identified yet. \(^\text{23}\)

Another possible cause is the mycobacterial infection, serological evidence supports that there is an increase production of anti-galactosyl IgG antibody triggered in response to protein p38, specific from mycobacteria in these patients. \(^\text{17,18,24}\)

Despite these observations, we still know little about features of the pathogenesis and etiology of these two diseases. Attention should be paid to extraintestinal complications such as TA, if there is a discrepancy between acute phase reactants and gastrointestinal symptoms in IBD patients. For that reason, a recent study suggested that non-invasive modalities including ultrasonography, CT, MRI, and fluoro-o-glucose-positron emission tomography (FDG-PET) can provide a diagnosis of TA early in the course of the disease. \(^\text{25}\)

Corticosteroids and immunosuppressive treatment could be used in both diseases, although some patients may also require surgical or endovascular revascularization procedures.

In our case, we used a combination therapy of oral corticosteroid at an initial dosage of 1 mg/kg/day and methotrexate (10 mg/m\(^2\)/week). After the initial 4 weeks, we slowly tapered the steroid to 0.5 mg/kg/day, which was successful.

There are a few reports of revascularizations procedures, being catheter-based interventional treatment the
most used, with encouraging results,\textsuperscript{36} which is preferably performed when the disease is not in an active phase.

In conclusion, our report indicates that patient suffering from IBD, can suffer from the rare coincidence for TA, even more if there is a previous history of refractory CD and there is a discrepancy between inflammatory markers and gastrointestinal symptoms. History taking, physical examinations, including measuring of bilateral blood pressure and pulses, ischemic signs and detection of systolic ejection murmur, are important for early diagnosis of TA in EC patients. Therefore begin as soon as possible with an optimal choice of therapy, induce and sustain remission, reaching optimal circumstances for interventional revascularization procedures, thus preventing severe complications, such as renal hypertension in this case, and raising awareness of a significant problem in the clinical setting.

References