

Coexisting Crohn's Disease and Takayasu's Arteritis in Two Patients Treated with Anti-TNF- α Therapies

S. Ratuapli^a M. Mazlumzadeh^b S. Gurudu^a S. Money^c
R. Heigh^a

Divisions of ^aGastroenterology, ^bRheumatology and ^cVascular Surgery, Mayo Clinic Arizona, Scottsdale, Ariz., USA

Key Words

Crohn's disease · Takayasu's arteritis · Coexisting · Anti-TNF alpha

Abstract

Crohn's disease (CD) and Takayasu's arteritis (TA) are inflammatory granulomatous autoimmune disorders. Simultaneous occurrence of CD and TA in the same individual is rare. We report two cases treated with biologic agents. Case 1: A 16-year-old male presented with abdominal pain, nausea, vomiting. CT angiogram showed thickening of the terminal ileum, wall thickening and narrowing of multiple large and medium arteries including aorta and left common carotid. Colonoscopy with biopsy of the stenotic ileocecal valve confirmed CD. Resected carotid artery pathology was consistent with TA. Treatment was initially begun with prednisone, then methotrexate was started followed by infliximab. Due to side effects, methotrexate was switched to azathioprine. He remained asymptomatic. Case 2: A 38-year-old male with well-characterized Crohn's ileocolitis for 15 years, who had been treated with prednisone, mesalamine, sulfasalazine, and azathioprine presented with chest, upper back and abdominal pain. CT angiogram showed vasculitis of large and medium arteries, with stenosis of the right renal artery, and wall thickening of the sigmoid colon. He was diagnosed with TA. He underwent treatment with infliximab and adalimumab on different occasions, which were later discontinued due to fever, bacteremia and complications from sepsis. He remained on prednisone and azathioprine. In these two patients with both CD and TA the diagnoses were confirmed by imaging and pathologic findings. Both patients developed vascular complications. Tumor necrosis factor inhibitor therapy was effective in one patient but discontinued in the other due to infection. Further research into the association of CD and TA may provide clues to their etiologies and guide effective interventions.

Introduction

Takayasu's arteritis (TA) and Crohn's disease (CD) are chronic inflammatory granulomatous autoimmune disorders that lead to characteristic manifestations. The exact etiologies of these diseases remain unknown. CD predominantly affects the gastrointestinal tract, and various hypotheses concerning the underlying pathology have been proposed, ranging from environmental [1], genetic [2], infections [3], autoimmune processes [4] to a defect in autophagy [5]. CD appears to be more prevalent in Caucasian populations, but recent reports have shown a rising incidence in Asian populations [6]. TA is a large vessel vasculitis predominantly affecting the aorta and its main branches. It usually presents in young adults. The chronic inflammation of unknown etiology affecting the arteries may lead to stenosis, occlusions, dilatations and aneurysms of affected vessels [7]. Cell-mediated autoimmunity leading to granulomatous inflammation is believed to represent the most probable pathologic cause of the disease. TA is more prevalent in Asia than in Western countries [8]. Simultaneous occurrence of these two diseases in the same individual is rare. We report two new cases seen in our institution.

Case 1

A 16-year-old male with a past medical history of thalassemia trait and recent diagnosis of hypertension presented with complaints of abdominal pain, nausea, vomiting, constipation and weight loss. He did not have any diarrhea, hematochezia or melena. The work-up for abdominal pain prompted CT angiogram imaging that revealed marked thickening of the terminal ileum and decreased uptake and atrophy of the left kidney, significant wall thickening and narrowing of the left common carotid, right common and internal carotid and subclavian and axillary arteries, and diffuse thickening of aortic arch and descending thoracic and upper abdominal aorta, with left renal artery occlusion ([fig. 1](#)). ESR and CRP were elevated. An MR enterography of the abdomen confirmed the mucosal thickening of the terminal ileum without bowel wall edema or additional sites of stenosis, hyperenhancement or fistulas. A colonoscopy was performed which revealed stenotic ileocecal valve with friable and inflamed terminal ileal mucosa and an ulceration ([fig. 2](#)). Biopsy from the terminal ileum confirmed the diagnosis of CD showing moderate active chronic ileitis. His laboratory studies were significant for elevated sedimentation rate of 23 and CRP of 27, positive antflagellin antibody (CBir1), but negative antisaccharomyces antibody (ASCA), outer membrane porin to *Escherichia coli* antibody (anti OmpC), lupus anticoagulant and anticardiolipin antibodies.

Prednisone 60 mg daily was started. Meanwhile, he developed retinal and cerebral ischemic episodes, leading to transient visual loss and syncope, for which he underwent ascending aorta to left common carotid artery bypass grafting. The resected carotid artery pathology was consistent with TA. Methotrexate was added. He did not have any significant relapse or symptoms of active CD other than intermittent abdominal pain. However, he suffered another episode of syncope with dehydration leading to thrombotic occlusion of his aortocarotid bypass graft requiring thrombectomy and revision of the graft. Infliximab was started to intensify his therapy. Methotrexate was later discontinued due to side effects and azathioprine was started instead. Prednisone was gradually tapered off. He remained asymptomatic as both his CD and TA remained under good control for twelve months.

Case 2

A 38-year-old male with a past medical history of hypertension and mild renal insufficiency presented with abdominal pain, diarrhea and chest pain. CD had been diagnosed 15 years prior to presenting to our institution by means of colonoscopy with biopsy. Review of reports from prior examinations revealed that CD was initially active in the colon, but later involved the small intestine as well. There was no previous history of strictures or fistulas or such findings during further evaluation in our institution. During the past 15 years he had been treated with prednisone, mesalamine, sulfasalazine and azathioprine. He had been on infliximab for 1 year when he developed chest, upper back and abdominal pain and noted to have ectasia of the descending aorta. Infliximab was discontinued 6 months later due to fever, bacteremia, and acute renal failure. He had remained on prednisone and

azathioprine chronically. The CD appeared to be inactive, except for episodic diarrhea without any hematochezia.

His abdominal imaging revealed thickening and paraaortic stranding of the abdominal aorta and wall thickening of the sigmoid colon, but also bilateral renal artery stenosis, which prompted further imaging of the chest and neck. TA was diagnosed when the CT angiogram showed wall thickening of the aortic arch, abdominal aorta, left subclavian and common carotid arteries, with sigmoid colon wall thickening (fig. 3). His laboratory studies were remarkable for leukocytosis, elevated CRP and normal sedimentation rate, but negative antinuclear antibody (ANA), p-ANCA (antinuclear cytoplasmic antibody), antFLAGELLIN antibody (Cbir1), antisaccharomyces antibody (ASCA), outer membrane porin to *Escherichia coli* antibody (antiOmpC), hepatitis A, B and C serologies. When follow-up imaging showed severe bilateral renal artery stenoses and renal atrophy, an aorto-birenal bypass grafting was performed. Adalimumab was started 6 months later due to persistent inflammation and elevated ESR and CRP despite prednisone and azathioprine therapy. Three weeks later he sustained sepsis, thrombosis of the graft, and renal failure requiring dialysis. Adalimumab was discontinued. He remained on prednisone and azathioprine thereafter and has remained stable for eight months.

Discussion

CD, being an inflammatory bowel disease, is associated with extraintestinal manifestations and other autoimmune disorders with a higher prevalence than ulcerative colitis [9]. Vasculitis, predominantly of the mesenteric vessels, has been suggested as a possible etiologic cause for intestinal manifestations, leading to ischemic damage and multifocal infarctions of the bowel wall, although granulomatous inflammation of the bowel wall generally does not correspond to the site of vasculitis [10]. Increased thrombophilia associated with inflammatory bowel disease can lead to regional or systemic complications of infarctions, thrombosis and embolism.

TA is a chronic idiopathic large vessel vasculitis of the aorta and/or its branches. Histopathological diagnosis of TA is difficult due to the involvement of major blood vessels. Hence imaging modalities like angiography, CT and MRI are being increasingly used as diagnostic techniques for TA [11]. Pathology of a resected artery was helpful in one of our patients, while the imaging studies were the main modes of diagnosis in both patients.

Simultaneous occurrence of these two diseases in the same individual is rare, but is being increasingly reported in part owing to heightened awareness and better access to superior diagnostic imaging. Similarities in the presentation of abdominal symptoms, especially abdominal pain [12] and gastrointestinal bleeding in both these diseases might delay or confound the diagnosis of one or the other. Granulomatous vasculitis due to cell-mediated injury is the common pathophysiological mechanism seen in both conditions, suggesting that simultaneous occurrence is more than just a coincidence. The underlying inflammatory process in both diseases appears to be influenced by cytokines such as tumor necrosis factor α (TNF- α) and interleukins including IL-6, IL-8, IL-12 and IL-18. HLA genotype links and even infectious agents such as *Mycobacterium tuberculosis* [13] have been implicated as common etiologies, but to date no definite etiological associations have been identified.

Review of published reports of coexisting CD and TA points to CD preceding TA in 88% of cases in the literature, with the age at diagnosis of CD ranging from 10 to 31 years and TA from 14 to 33 years [14]. While age was similar in both of our patients, CD preceded TA in one patient, but was diagnosed simultaneously in the other. Corticosteroids, immunosuppressive agents and TNF- α inhibition have been effective in the management of both CD and TA [15]. However, the current literature does not

provide enough information about the management outcomes of this group of patients with coexisting diseases.

In our patients, prednisone was initially started, followed by steroid-sparing agents and ultimately biologic therapy. Stenotic and thrombotic complications appear to develop not infrequently in this group of patients as evidenced by graft thrombosis and occlusion in both of our patients. While our first case had an excellent response to biologic therapy and remained asymptomatic, the second case responded poorly to TNF- α therapies and was associated with recurrent infectious complications.

In summary, in these two patients with both CD and TA the diagnoses were confirmed by imaging and pathologic findings. Both patients developed vascular complications. Cytokine- and interleukin-mediated granulomatous inflammation appears to be the likely common pathologic pathway in these two diseases. TNF- α inhibition targeting this common pathway was effective in one patient but discontinued in the other due to infection. Further research into the association of CD and TA may provide clues to their etiologies and guide effective interventions.

Fig. 1. Aortic arch angiogram of case 1 showing stenoses of multiple large arteries of the aorta.

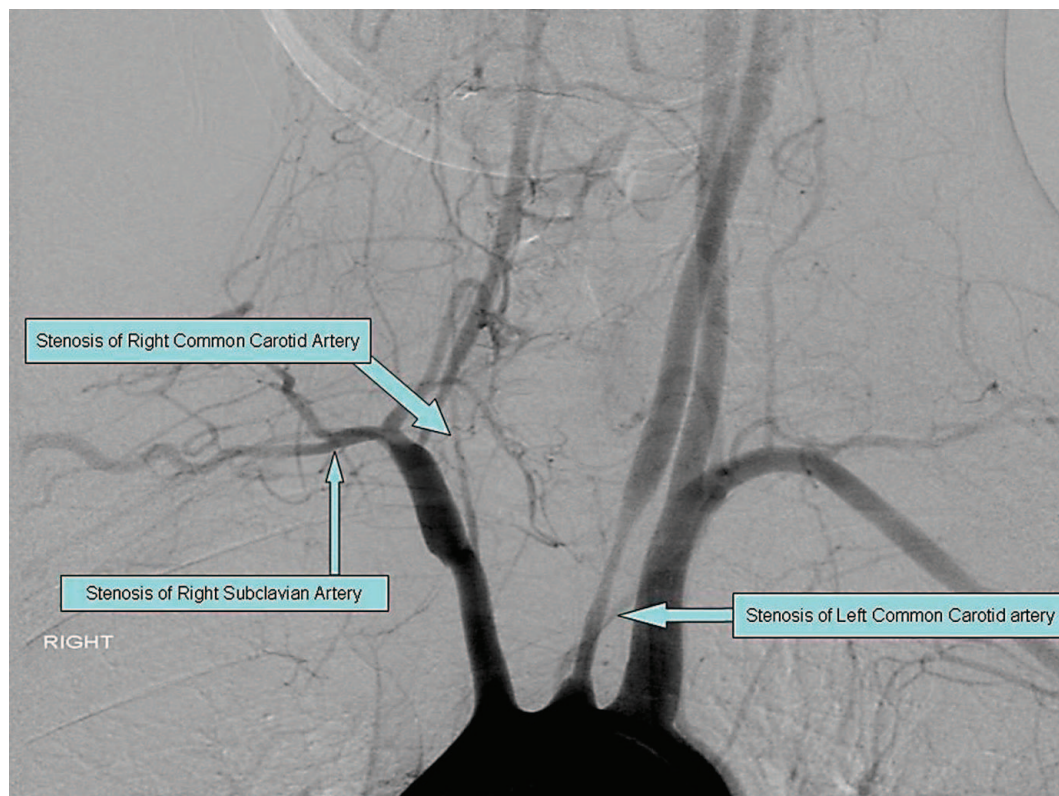


Fig. 2. Colonoscopy of case 1 showing stricture at the terminal ileum.

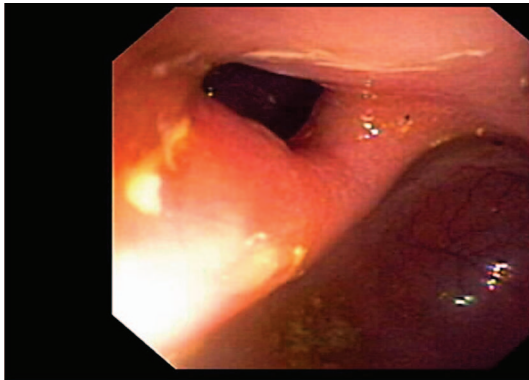


Fig. 3. Angiogram showing stenoses of the right renal artery in case 2.



References

- 1 Shanahan F: Crohn's disease. *Lancet* 2002;359:62–69.
- 2 Gaya DR, et al: New genes in inflammatory bowel disease: lessons for complex diseases? *Lancet* 2006;367:1271–1284.
- 3 Weinstock JV, Elliott DE: Helminths and the IBD hygiene hypothesis. *Inflamm Bowel Dis* 2009;15:128–133.
- 4 Marks DJ, Segal AW: Innate immunity in inflammatory bowel disease: a disease hypothesis. *J Pathol* 2008;214:260–266.
- 5 Klionsky DJ: Crohn's disease, autophagy, and the Paneth cell. *N Engl J Med* 2009;360:1785–1786.
- 6 Sood A, Midha V: Epidemiology of inflammatory bowel disease in Asia. *Indian J Gastroenterol* 2007;26:285–289.
- 7 Tann OR, Tulloh RM, Hamilton MC: Takayasu's disease: a review. *Cardiol Young* 2008;18:250–259.
- 8 Bulum J, et al: Takayasu's arteritis and chronic autoimmune thyroiditis in a patient with type 1 diabetes mellitus. *Clin Rheumatol* 2005;24:169–171.
- 9 Bardella MT, et al: Autoimmune disorders in patients affected by celiac sprue and inflammatory bowel disease. *Ann Med* 2009;41:139–143.
- 10 Wakefield AJ, et al: Pathogenesis of Crohn's disease: multifocal gastrointestinal infarction. *Lancet* 1989;2:1057–1062.
- 11 Gotway MB, et al: Imaging findings in Takayasu's arteritis. *AJR Am J Roentgenol* 2005;184:1945–1950.
- 12 Zamani F, et al: Abdominal pain as presentation of Takayasu's arteritis in an adolescent male patient. *MedGenMed* 2006;8:69.
- 13 Szewczuk MR, Depew WT: Evidence for T lymphocyte reactivity to the 65 kilodalton heat shock protein of mycobacterium in active Crohn's disease. *Clin Invest Med* 1992;15:494–505.
- 14 Reny JL, et al: Association of Takayasu's arteritis and Crohn's disease. Results of a study on 44 Takayasu patients and review of the literature. *Ann Med Interne (Paris)* 2003;154:85–90.
- 15 Hoffman GS, et al: Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004;50:2296–2304.