The Coexistence of Crohn’s Disease and Takayasu Arteritis: Diagnosis and Treatment of Combined Disease in Three Patients

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Background and Aims: Crohn’s disease is an inflammatory bowel disease classically causing granulomatous, transmural inflammation of the bowel wall, producing abdominal pain, obstruction, and fistula formation. Takayasu arteritis is a chronic granulomatous vasculitis that causes inflammation and stenosis of large and medium-sized arteries including the aorta and its primary branches. The aim of this case series is to describe three cases of coexisting Crohn’s disease and Takayasu arteritis and the response to anti-tumor necrosis factor therapy at a tertiary care medical center. Methods: A case report design was used. Results: We report on three patients with coexisting Crohn’s disease and Takayasu arteritis. The diagnosis of Crohn’s disease was made by combining patient symptoms, laboratory data, radiographic imaging, endoscopic evaluation and pathological evaluation of luminal mucosal biopsy. All of these patients also met classification criteria for Takayasu arteritis as defined by the American College of Rheumatology. Unique to this case report is the treatment of these patients with infliximab for their combined disease. Conclusions: Evidence is building in the medical literature for a subgroup of patients with coexisting Crohn’s disease and Takayasu arteritis. A common autoimmune etiology has been hypothesized. The three patients in this report received infliximab therapy, which has previously not been described in the literature as treatment for patients with these combined diseases. We discuss the parallel pathophysiology and treatment of these diseases and explore the role of biologic agents as therapy for patients who have coexisting Crohn’s disease and Takayasu arteritis.

INTRODUCTION

Takayasu arteritis (TA) is a chronic granulomatous vasculitis that primarily affects the aorta and its primary branches, resulting in thickening of the walls of affected arteries (1,2). This disease results in an inflammatory process that manifests clinically with a wide range of systemic symptoms (3). Symptoms may include fatigue, weight-loss, and low-grade fever along with cool pulseless extremities, differential blood pressures in the left and right arm, claudication, hypertension, and bruits secondary to the stenotic lesions. Crohn’s disease (CD) is a granulomatous, transmural inflammation of the gastrointestinal tract most commonly affecting the ileum and cecum but may affect any portion of the small intestine and colon.
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It commonly presents with abdominal pain, fevers, and diarrhea and may result in strictures and fistulae (4,5). The pathophysiology of CD and TA has not been completely elucidated; autoimmune dysfunction appears to be a component of each. Increasingly, there is discussion in the literature of both of these diseases coexisting in patients (6–9). We present three cases of patients with coexisting CD and TA. Our case series is the first report of treatment with infliximab maintenance therapy for combined CD and TA. The overlapping pathophysiology and treatment of these diseases are discussed.

CASE PRESENTATIONS

Case 1
A 24-year-old female, originally from Puerto Rico, began to have diffuse, crampy intermittent abdominal pain in April 2007. Symptoms worsened until she presented in July 2007 at the emergency department. The patient’s main complaint was severe abdominal pain; however, she also had complaints of neck pain, chest pain, and fatigue. Vital signs and basic laboratory evaluation (complete blood count, electrolytes, and liver panel) were all within normal ranges. Computed tomographic (CT) scan of the abdomen and pelvis did not show any findings to explain her symptoms. She underwent colonoscopy in July 2007 that revealed ulceration in the terminal ileum. Biopsies from this terminal ileum ulceration were noted to demonstrate active inflammation consisting of neutrophilic infiltration of the epithelium with surface erosion and cryptitis, as well as chronic features consisting of architectural distortion and increased basal lymphoplasmacytic inflammation. Granulomas were present. Overall, these biopsies were concerning for CD. Prometheus IBD-7 serologies (Prometheus Laboratories, San Diego, CA, USA) were also consistent with the diagnosis of CD (positive values included anti-CBir1 at 37.1 EU/mL and autoantibody ELISA at 16.6 EU/mL, as well as a result algorithm suggestive of CD). She was started on budesonide and responded with improvement of symptoms. However, in August 2007, after tapering off budesonide, she again was hospitalized for recurrent severe abdominal pain. A CT scan of the abdomen was concerning for partial small bowel obstruction at the level of the terminal ileum. The patient was started on a course of prednisone and was treated with supportive care. However, she began to have significant hypertension and hypokalemia. Workup with magnetic resonance angiography (MRA) demonstrated high-grade stenosis of the left renal artery. There was also a high-grade stenosis of the proximal celiac artery and proximal superior mesenteric artery. Other vessels of the chest and neck demonstrated patent vasculature on MRA at this point. Her erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were within normal limits, but she was on systemic steroid therapy at the time. She had a percutaneous angioplasty of the left renal artery and began to respond to steroid therapy allowing her discharge home. During a follow-up visit in October 2007, a new bruit was auscultated in the area of the left subclavian artery. Follow-up CT angiogram revealed a 75% stenosis of the left subclavian artery had developed since the normal MRA in July 2007. She also continued to experience partial small bowel obstruction when attempts were made to taper steroids below 10 mg per day. Thus, in January 2008, the decision was made to start the patient on biologic therapy with infliximab (regimen defined as an initial 5 mg/kg dose followed by infusions at two weeks, six weeks and then every eight weeks). The patient has been on infliximab therapy for four months so far. The addition of this therapy has allowed the steroids to be discontinued. She has gained 15 lbs. of weight and has resumed exercising four times per week at the gym.

Case 2
A 49-year-old Caucasian female presented in August 2006 to our vascular surgery clinic for follow-up of a superior mesenteric artery aneurysm identified on an outside CT. She had been diagnosed with CD in 1987 after having a terminal ileal resection when presenting with right lower quadrant abdominal pain. The surgical specimen revealed pathologic changes in the terminal ileum consistent with CD. She had done well with only minimal symptoms related to her CD until 2000 when she began to have a more severe clinical course. Of (continued on page 54)
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Note, the superior mesenteric artery was normal on a CT in 2002. She was tried on numerous medical therapies including courses of prednisone, antibiotics, mesalamine, budesonide and was currently on mercaptopurine (6-MP). She did well for several months, then again had a CD flare on 6-MP. When we evaluated the patient in our GI clinic in 2006, she was experiencing up to six bowel movements per day associated with episodes of significant right lower quadrant pain at times. The presence of active CD was confirmed on CT enterography performed with positron emission tomography and 18-fluorodeoxyglucose (PET-FDG) in the mid- and distal-ileum. A colonoscopy had been performed one year prior showing inflammation in the terminal ileum with biopsies revealing inflammatory changes consistent with active CD. Further vascular evaluation with a CT scan at our institution again showed inflammation and thickening of the superior mesenteric artery, but no aneurism was noted. Serologic markers of inflammation, including CRP and ESR were within normal limits; however, she was on steroids at the time these labs were drawn. She did have some related symptoms of fatigue and lethargy. Our rheumatology colleagues felt this patient’s presentation overall was consistent with TA. Due to persistent evidence of superior mesenteric artery inflammation despite significant immunosuppression, and due to poorly controlled CD, she was started on infliximab therapy (5 mg/kg dose). She has done remarkably well on this infliximab therapy. A repeat CT scan showed resolution of the superior mesenteric artery inflammation. The patient’s CD symptoms also significantly improved, with resolution of abdominal pain and diarrhea.

Case 3

A 32-year-old Caucasian female was referred to our outpatient clinic for evaluation of poorly controlled CD in 2006. She first began to have symptoms of CD in 2004, when she began to have increased stool frequency and postprandial loose stools. Progressively, she developed right lower quadrant abdominal pain. At this time, she developed symptoms of claudication while climbing stairs and was found to have decreased pedal pulses. A diagnosis of TA was made after she was found to have inflammation and narrowing of the infrarenal abdominal aorta on a CT angiogram. Colonoscopy was performed in 2004 due to her GI complaints, but the colon was torturous and visualization was only performed to the ascending colon. The patient’s symptoms related to vascular insufficiency did not respond to steroids and she had surgery resulting in placement of an abdominal aortic graft distal to the renal arteries. The surgical specimen showed inflammatory changes, consistent with TA. Further GI workup was deferred while the patient underwent treatment for the vascular disease. Her claudication and other symptoms related to TA significantly improved after surgery. However, her gastrointestinal symptoms continued to progress postoperatively, and over the course of 2005 she was empirically placed on additional steroid courses. Small bowel follow-through was performed and two distal ileal strictures

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were noted. She was started on azathioprine and referred to our clinic. At her initial clinic at the University of Florida in May 2006, she continued to have frequent small caliber stools, generalized abdominal pain, and she had weight loss of over 20 pounds since 2004. CT enterography with PET-FDG was obtained to verify the location and activity of her CD and to assess for vascular inflammation (Figure 1). This scan showed extensive active CD throughout the terminal ileum, a terminal ileal stricture and an area of “matted” bowel in the right lower quadrant. This scan also showed thickening at the base of the aortic arch with FDG uptake consistent with active TA disease. Colonoscopy was performed and revealed an ileocolonic fistula in the ascending colon surrounded by pseudopolyps. Biopsies of this area revealed active colitis on pathology examination. A solitary ulcer in the hepatic flexure was also noted and demonstrated only a focal mucosal erosion on pathology. The terminal ileum could not be completely intubated due to the presence of a stricture, but ileum distal to the stricture appeared normal macroscopically. Biopsies revealed active inflammatory infiltrate and architectural distortion of the terminal ileum consistent with CD. The patient began to have significant abdominal pain shortly after colonoscopy consistent with CD flare, despite continued immunosuppression with steroids and azathioprine. She was admitted to the hospital, and after careful observation, was started on infliximab therapy at 5 mg/kg. Following this initial dose of infliximab, her symptoms significantly improved with decreased frequency of bowel movements, relief of abdominal pain, and ability to tolerate solid food. Three weeks after discharge, she again developed right lower quadrant pain and was hospitalized at her local hospital. She was found to have the “inflammatory mass” in the right lower quadrant on CT scan, requiring a terminal ileum resection and a right hemicolectomy. The surgical specimen showed significant active inflammation of this area consistent with CD. She continued on infliximab after surgery for another six weeks, and then developed an allergic response to infliximab necessitating discontinuing this therapy. She continued on budesonide and azathioprine until September 2007, with only partial control of CD symptoms. She was then started on adalimumab and has not had further flares of her CD or TA. She has been able to discontinue her steroids and is able to work and partake in her normal daily activities.

DISCUSSION AND CONCLUSIONS
The three patients with coexisting CD and TA presented in this series were seen at a single center in 2006 and 2007. In one case the diagnosis of CD preceded the development of TA by many years, in the other two, the symptoms of TA and CD presented simultaneously. In all of the cases the diagnosis of CD was made by standard radiographic, endoscopic, and pathological criteria. All three patients also met classification criteria for TA as defined by the American College of Rheumatology (2). There have been at least 29 reported cases of patients with coexisting CD and TA in the medical literature to date (7). Three different cohorts of patients with TA have been found to have CD in a much greater frequency than would be expected by random chance. In a French series, by Reny, et al four patients in a cohort of 44 patients with TA also had CD (8). Hall, et al reported on 32 North American patients with TA and found two to have coexisting CD (9). A longitudinal study of 60 patients with TA, done by Kerr, et al found two patients suffered from CD, and an additional two patients had been diagnosed with ulcerative colitis (10). These three studies demonstrate a prevalence of CD in patient’s with TA ranging from 3% to 9%, making it significantly higher than the prevalence of CD reported in the general population at around 0.2% (11,12). Thus, based on these three patient cohorts, CD would be expected to be 15 to 45 times more prevalent in a TA patient population than in the general population. The small number of patients with coexisting disease makes it difficult to draw further statistical conclusions; however, it does appear that patients with coexisting CD and TA are more likely to exhibit systemic symptoms of fever, weight-loss, and fatigue than the patients having TA alone (8).

There are a number of presenting features common to both diseases. Both diseases share a female predominance (1,4,5). TA is nine times more common in women, and CD is 1.2 times more common in women (6). The female predominance suggests a pos-
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Possible influence of sex hormone or estrogen exposure, but the exact mechanism of this effect is still largely unknown (13–16). Both CD and TA have a typical age of onset between 10 to 40 years of age, with most patients presenting with symptoms in the second or third decade of life (6). Both diseases may also present with skin manifestations such as pyoderma gangrenosum or erythema nodosum (10,17–19).

There is growing evidence that suggests TA and CD share an overlapping autoimmune etiology and pathophysiology. The pathogenesis of both diseases includes predominately type 1 helper T cell (TH1) lymphocytes (20). This is in contrast to ulcerative colitis which is less frequently associated with vasculitis and for which lymphocytic infiltrates are more similar to a type 2 helper T cell (TH2) response (20). Granulomatous inflammation is characteristic of both CD and TA. There is histopathologic evidence to support the idea that vasculitis may be important in the pathophysiology of CD as well as TA. CD has been associated with single nucleotide polymorphisms in NOD2, IL23R, ATG16L1, and others (23–29). We are not aware of investigations into an association of these CD associated mutations with TA.

As with many immune mediated disorders, it is not surprising that both CD and TA would respond to similar treatment regimens. Familiar medical therapies, which have been reported in the literature as treatment for CD include systemic corticosteroids, methotrexate, azathioprine, and mycophenolate mofetil (30). These same drugs are often used as medical therapy for TA. Steroids have been a mainstay of therapy for TA. Methotrexate has been evaluated for TA, with one trial of 16 patients demonstrating an 81% remission rate with methotrexate treatment (31). Azathioprine has also been used for treatment of TA, often in combination with steroids, and has shown some promise (32). There is also some data demonstrating mycophenolate mofetil as an effective therapy for TA (33).

Recently, there has been increased interest in using biologic agents, such as infliximab for the treatment of TA. For over 10 years, there has been published data, showing the benefit of infliximab for CD (34,35). However, it was only in 2004, that Hoffman, et al published the first pilot study of anti-tumor necrosis factor (anti-TNF) agents for the treatment for TA (36). In this uncontrolled series, 15 patients that required high dose steroids to maintain remission, were treated with infliximab or entanercept, and initial improvement was noted in 14 of 15 patients. Sustained response was noted in 10 patients who were able to completely discontinue steroids, although dose escalation was needed in order to maintain TA disease remission. Several other case reports support the efficacy of anti-TNF agents in TA (37,38). However, there has not been a large scale trial conducted to show the efficacy of biologic agents in TA. In a 2008 case report, a young woman with CD for five years had a CD flare and aortitis observed on CT after missing one infliximab infusion. Both the CD and aortitis responded to an infliximab dose escalation (39). Of note, this patient only had aortitis and was not diagnosed with TA. The three patients described in this case series represent the first reported cases of combined active TA and CD, who were successfully treated with anti-TNF therapy. Treatment with anti-TNF agents should represent a useful adjunct to existing therapies, which can be used in patients with combined TA and CD. As further investigation is undertaken to determine the linkage between CD and TA, additional treatment modalities may come to light, which will be of benefit in both disease processes. Those treating CD or TA should be vigilant for signs and symptoms suggesting the development of this uncommon association.

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