Large-Vessel Granulomatous Vasculitis in Crohn's Disease

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Case presentation

A 28-year-old African-American female with a past medical history of Crohn's disease and associated arthritis was evaluated for chest pain of 5-month duration that had become worse over the previous week. Her past medical history was significant for Crohn's disease diagnosed 7 years earlier when she presented with nonbloody diarrhea after a trip to Kenya. She underwent a colonoscopy that confirmed

the diagnosis, and she was treated with mesalamine and steroids for 1 year at an outside institution. She had one flare of her bowel disease 2 years later, which required hospitalization for 2 days and was treated briefly with oral steroids. She also underwent a liver biopsy because of abnormal liver enzymes. This revealed primary sclerosing cholangitis which was not specifically treated at that time.

Ten months prior to this presentation, the patient was admitted with a threatened abortion at 13 weeks of gestation along with an asymmetric polyarthritis of the fingers, wrists, elbows, shoulders, and ankles. During her hospitalization, she was noted to have a rash, characterized as minute follicular pustules, on the right side of her face and right upper extremity. She did not have any bowel symptoms at this time. Diagnostic workup revealed antiproteinase 3 (anti-PR-3) antibody of 536 AU/ml (normal <19 IU), rheumatoid factor (RF) of 24 IU/ml (normal 0–20 IU), erythrocyte sedimentation rate (ESR) of 139 mm/h (normal 0–20 mm/h), and C-reactive protein of 11.9 mg/dl (normal 0.30–0.80 mg/dl). A skin biopsy of the rash demonstrated vesiculopustular pyoderma gangrenosum consistent with her underlying Crohn's disease. Antinuclear antibodies, anti-double-stranded DNA antibodies, anti-streptolysin O antibody, viral hepatitis serologies, anticyclic citrullinated peptide, and human immunodeficiency virus testing were negative. She was started on 100 mg intravenous (IV) hydrocortisone three times daily for 3 days followed by 60 mg oral prednisone which was tapered off over the next 4 weeks. She also received two doses of 5 mg/kg infliximab 2 weeks apart.

Six weeks later (gestational week 19), the patient presented with chest pain, arthritis, temperature of 38.7°C, and pulse of 130 beats per minute. A workup to reveal a source of infection was performed and was found to be negative. Also, an electrocardiogram, echocardiogram, and

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Each author certifies that his or her institution has approved the reporting of this case and that all investigations were conducted in conformity with ethical principles of research.

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computerized axial tomography of the chest with IV contrast were obtained and were found to be within normal limits. She was diagnosed with serositis and treated with 125 mg IV methylprednisolone for 2 days followed by 16 mg oral methylprednisolone every 8 h. She was discharged to follow-up with an outside rheumatologist. She continued to receive 5 mg/kg infliximab every 8 weeks.

Two months later (gestational week 26), she again presented with chest pain, shortness of breath, tachycardia, and a flare of her arthritis. The above workup was repeated and was again negative. She was given 80 mg Depo Medrol intramuscularly once followed by 16 mg Medrol every 8 h and one additional dose of infliximab at 5 mg/kg. She underwent a normal vaginal delivery at 38 weeks of gestation and continued to follow-up with an outside rheumatologist.

Five months postpartum, she presented with chest pain of 1-week duration. She described the chest pain as localized over the left chest and between her epigastrium and neck. The pain radiated to her left arm and her back. It was exacerbated by lying down and improved with sitting up. On review of systems, she reported shortness of breath and intermittent palpitations. She also reported a sore throat 1 week prior. Recent laboratory testing done by an outside physician reportedly indicated that she might have hyperthyroidism. She denied fevers, chills, night sweats, weight loss, oral or genital ulcers, alopecia, Raynaud's phenomenon, sicca symptoms, gastrointestinal or urinary symptoms.

The patient's medications at the time of admission included 8 mg oral methylprednisolone in the morning and 4 mg in the evening and 5 mg/kg infliximab every 8 weeks. She denied noncompliance with her medications or allergies to medications. She was a former high school teacher and lived with her mother and 5-month-old son. She did not report any past or present smoking, alcohol, or illicit substance use.

On physical examination, vital signs were within normal limits and blood pressure measurements were equal in both arms. Cardiac, pulmonary, abdominal, and neurological examinations were normal. No bruits were noted and there was no synovitis. Abnormal laboratory studies included a WBC of 11.2 K/l with 75% neutrophils, ESR of 132 mm/h, C-reactive protein of 20.17 mg/dl, alkaline phosphatase of 160, protease Ig3 of 120 AU/ml, and positive hepatitis B surface antigen (Tables 1 and 2). The electrocardiogram was remarkable only for sinus tachycardia as well as subtle abnormalities in several ST segments and PR intervals (Fig. 1). The echocardiogram was normal.

Radiological findings

Chest radiograph was normal. A computerized tomography (CT) scan of the chest was repeated and is compared to the one from 8 months prior at week 19 of pregnancy (Figs. 2 and 3). There was an interval development of an ascending aortic aneurysm and diffuse wall thickening involving the

Table 1 Significant laboratory tests

Laboratory test	Value	Reference range
White blood cells	11.2	3.4–11.2 K/ul
Differential	N-75.9%, L-17.4%	N-40–74%, L-19–48%
Hemoglobin	9.4	11.7–16.0 g/dl
Platelets	354	150–450 K/ul
Sodium	139	133–147 mmol/l
Potassium	3.9	3.2–5.2 mmol/l
Chloride	102	94–110 mmol/l
Carbon dioxide	26	22–32 mmol/l
Blood urea nitrogen	7	5–25 mg/dl
Creatinine	0.6	0.5–1.5 mg/dl
Glucose	119	70–105 mg/dl
Calcium	9.2	8.5–10.5 mg/dl
Total protein	6.6	5.5–8.0 g/dl
Albumin	2.5	3.0–5.0 g/dl
Total bilirubin	0.6	0.2–1.3 mg/dl
Alanine aminotransferase	34	0–45 U/l
Aspartate aminotransferase	32	0–45 U/l
Alkaline phosphatase	160	25–95 U/l
Erythrocyte sedimentation rate	132	0–20 mm/h
C-reactive protein	20.17	0.30–0.80 mg/dl
Thyroid stimulating hormone	1.51	0.34–5.64 mU/l
Creatinine kinase	40	46–295 U/l
Troponin I	0.02	0.01–0.04 ng/ml

aorta and great vessels. The ascending aorta measured 4.8 × 5.3 cm at the level of the right main pulmonary artery where previously it was 3.4 × 3.1 cm. The aortic arch measured 3.8 cm and previously measured 2.0 cm. There was no vascular dissection or pulmonary embolus. The lung parenchyma was normal in appearance.

Subsequently, ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography scan was performed (Fig. 4). The images were fused with computerized tomography for anatomic correlation (Fig. 5). The aorta showed abnormal mural FDG uptake from its origin to the level of the diaphragm. Similarly, there was an abnormal uptake in the aortic branch vessels of the neck. The above findings were felt to be consistent with large-vessel vasculitis.

Pathological findings

Given the rapid development of the aortic arch aneurysm and the risk of rupture, cardiothoracic surgery consultation was obtained and urgent aortic repair was scheduled. The aortic arch showed irregular mural thickening and inflammation in the outer two thirds of the aortic media extending to the adventitia. Both vague and well-formed noncaseating granulomata were identified, characterized by histiocytes surrounded by mononuclear inflammatory cells (Fig. 6a, b). High-power view of a well-formed granuloma highlighted multinucleated giant cells characteristically seen in granulomatous large-vessel vasculitis (Fig. 6c). An elastin stain of the internal elastic lamina demonstrated disruption of the fibers by direct infiltration of inflammatory cells (Fig. 7). In

Table 2 Serologic laboratory tests

Laboratory test	Value	Reference range
Antinuclear antibody	Negative	Negative
Double-stranded DNA antibody	Negative	Negative
Anti-Smith antibody	0	0–49 U
Anti-Ro(SSA) antibody	0	<40 AU/ml
Anti La (SSB) antibody	0	<40 AU/ml
Rheumatoid factor	<20	<20 IU/ml
Anticyclic citrullinated peptide	0	<20 U
Myeloperoxidase IgG	0	<20 AU/ml
Protease 3 IgG	201	<20 AU/ml
Rapid plasma reagin test	Negative	Negative
Lyme antibody	Nonreactive	Nonreactive
Parvovirus IgM antibody	0.36	0.89 IV or less
Angiotensin-converting enzyme	17	9–67 U/l
Hepatitis B surface antigen	Negative	Negative
Hepatitis B surface antibody	Positive	Negative

summary, the histologic findings were consistent with a granulomatous vasculitis.

Rheumatologic discussion

Crohn's disease is a chronic inflammatory disorder that may present in any area of the gastrointestinal tract with symptoms that include abdominal pain, diarrhea, and weight loss. Subsequently, obstruction, fistulization, or abscess formation within the bowel may occur. The prevalence of Crohn's disease is estimated to be 10 to 90

per 100,000 individuals [1]. Extraintestinal manifestations of Crohn's disease are common. Nearly 5% of patients may develop arthritis, which is typically of two variants: axial or peripheral. Axial features include sacroiliitis and ankylosing spondylitis. Peripheral arthritis may be asymmetric and oligoarticular with predominant involvement of the knees or ankles or polyarticular with inflammation of the small joints of the hands. These patients tend to be negative for RF. Characteristic dermatologic findings in Crohn's disease include erythema nodosum or pyoderma gangrenosum. Ophthalmologic complications such as uveitis or scleritis have also been reported. Primary sclerosing cholangitis may also be seen, as reported in our patient [2]. Bowel wall histology in Crohn's disease is characterized by "skip lesions" or well-demarcated focal areas of ulceration and transmural inflammation. Approximately 50% of intestinal biopsies in Crohn's disease also show noncaseating granulomas [3].

In our patient with Crohn's disease, the presence of a granulomatous large-vessel vasculitis suggested a concomitant diagnosis of Takayasu's arteritis, giant cell arteritis, sarcoidosis, or possibly Behcet's disease. Takayasu's arteritis and giant cell arteritis are large-vessel granulomatous arteritides. Patients with giant cell arteritis tend to be older (age >50) with symptoms related to inflammation of the cranial branches of the aorta such as new headaches, temporal artery tenderness, and elevated inflammatory markers. Vascular manifestations of sarcoidosis are uncommon and can occur in either large, medium, or small vessels. Seven adult cases of large-vessel vasculitis in sarcoidosis have been reported. In six of these patients,

Fig. 1. Electrocardiogram. There is sinus tachycardia and subtle upsloping ST segment elevations in leads *V1*, *V4–V6*, and *avF* along with PR interval depressions in leads *I*, *II*, *avF*, *V2–V6* and PR elevation in lead *aVR*

Fig. 2. Axial image from contrast-enhanced computerized tomography (CT) scan. Normal-caliber ascending aorta 1 year prior to presentation (a) and marked dilatation of the ascending aorta on presentation (b)

there was concomitant involvement of both lung parenchyma and lymphadenopathy [4]. In Behcet's disease, vasculitis is usually of the small vessels although non-granulomatous inflammation of the ascending aorta has

been reported. Behcet's disease patients with aortitis frequently have ulcers, uveitis, or skin lesions which were not seen in our patient [5]. Aortitis secondary to inflammatory bowel disease or ankylosing spondylitis were additional considerations in our patient. Case reports, however, suggest that the aortitis in these conditions is limited to the aortic root and arch (sometimes resulting in aortic valve insufficiency or dissection) [6–9]. Aortic abnormalities can also result from genetic diseases of collagen and from infection. Our patient did not have clinical features or family history to suggest Marfan's syndrome, and the previously negative PPD and rapid plasma reagin testing argued against syphilis or tuberculosis. Although the patient was anti-PR-3 positive, her clinical and radiological findings were not consistent with Wegener's granulomatosis, which is a small-vessel vasculitis.

Takayasu's arteritis is a large-vessel vasculitis typically presenting in young females of reproductive age. Histologically, it is indistinguishable from giant cell arteritis but age of onset and location of inflammation are important differences. The incidence of this disease is estimated to be 2.6 cases per million in North America. Ongoing inflammation of the aorta and its branches leads to stenosis and aneurysm formation. Notable clinical features include vascular bruits, absent pulses, and claudication in the extremities. In early stages, the intimal lining is thickened with fibroblasts and smooth muscle cells. The outer two thirds of the media along with the adjacent adventitia are inflamed and contain an infiltrate composed of lymphocytes and giant cells. In the latter "burnt out" phase of the disease process, fibrosis and disruption of elastin occurs, leading to stenosis and aneurysmal formation. Necrotizing granuloma formation may also be seen [10].

Our patient's age, gender, radiographic findings, and the multinucleated giant cells within noncaseating granulomas seen on vessel pathology suggest a diagnosis of Takayasu's arteritis. Although the patient did not meet the 1990 American College of Rheumatology classification criteria

Fig. 3. Sagittal reformat images from chest CT scan. Ascending aortic aneurysm (a) and diffuse aortic wall thickening (b)

Fig. 4. Positron emission tomography. Increased uptake within the brachiocephalic, carotid, and subclavian vessels is seen (**a**). There is increased ^{18}F -fluorodeoxyglucose avidity in the wall of the ascending aorta (*short arrow*) and descending aorta (*long arrow*; **b**)

for Takayasu's arteritis (Table 3), her disease may have been in the acute inflammatory phase or modified by concurrent immunosuppressive therapy. There are 30 case reports in the literature of Crohn's disease and Takayasu's arteritis occurring in the same individual, although both diseases are rare [12].

Immunological discussion

Crohn's disease and Takayasu's arteritis share several features. Human leukocyte antigen (HLA) class I associations have been established for both: HLA-B52 and B39 in the case of Takayasu's and HLA-B27 in some patients with Crohn's disease [13]. Other common features include granuloma formation on pathology and responsiveness to anti-TNF therapy. In intestinal specimens of patients with inflammatory bowel disease, granuloma formation within small vessels has been seen [14]. These observations suggest that the two diseases may be part of the same immunologic spectrum rather than distinct clinical entities.

The etiology of Crohn's disease is unknown but both genetic and environmental processes have been implicated. Crohn's disease is generally thought to be caused by dysregulation of Th1- and Th17-mediated responses against bacterial antigens of the normal intestinal flora, resulting in loss of tolerance. Prominent cytokines driving Th1- and Th17-type autoimmunity include interleukin (IL)-12, IL-23, TNF- α , and IFN- γ [15].

Fig. 5. Positron emission tomography–computerized tomography. Sagittal (**a**) and axial views (**b**) reveal abnormal ^{18}F -fluorodeoxyglucose uptake within the large vessels

Fig. 6. Light microscopy. Low-power (a) and medium-power (b) views of aortic arch highlight the irregular thickening of the aortic wall and a collection of inflammatory cells forming a granuloma. High-power (c) view of aortic arch shows multinucleated giant cells within the granuloma (black arrow)

The innate immune system also plays a critical role in microbe defense in the gut. Under normal conditions, toll-like receptors on antigen-presenting cells in the luminal mucosa downregulate activation of epithelial cells. These antigen-presenting cells contain an intracellular detection

Fig. 7. Low- (a) and medium-power (b) view of elastin stain. There is disruption of medial elastic lamina by infiltration of inflammatory cells (black)

system for microbes called nucleotide-binding site/leucine-rich repeat proteins. Among these proteins are nucleotide oligomerization domains (Nod) 1 and 2 which recognize peptidoglycans (PDG) in bacterial cell walls. Nod2 is expressed predominantly in myelomonocytic cells and contains an LRR sequence which recognizes a fragment of PDG termed muramyl dipeptide. Nod2 oligomerizes and promotes downstream activation of nuclear factor (NF)- κ B pathway via the IKK complex. Three frequent mutations in the Nod2 gene increase susceptibility to Crohn's disease. Of

Table 3 The American College of Rheumatology 1990 criteria for the classification of Takayasu's arteritis [11]

Age at disease onset <40 years old
Claudication of the extremities
Decreased brachial artery pulse
Blood pressure difference >10 mmHg between arms
Bruit over the abdominal aorta or either of the subclavian arteries
Arteriogram abnormalities, namely narrowing or occlusion of the large arteries not secondary to atherosclerosis or other etiology

At least three of six criteria are needed for diagnosis. The classification criteria have a sensitivity of 90.5% and a specificity of 97.8%

particular interest is the frameshift stop codon at 1007 (1007 fs) mutation. This mutation was originally thought to confer a loss-of-function role upon the Nod2 gene, even though Crohn's disease patients are known to have increased NF- κ B activation in inflamed mucosal cells. Recent studies suggest that the mutation may actually confer a gain of function for Nod2 via its interaction with anti-inflammatory IL-10. The proposed mechanism is that Nod2 1007 fs mediates disruption of activation of IL-10 transcription via the transcription factor heterogenous nucleoribonuclear protein A1 [16].

While there have been no studies to date of the Nod2 gene mutation in large-vessel vasculitis, there are other autoimmune diseases associated with the Nod2 1007 fs mutation including the seronegative spondyloarthropathies [17] and graft-versus-host disease [18].

The pathogenesis of Takayasu's arteritis is even less well understood than that of Crohn's disease, although cell-mediated immunity is also of great importance. The inflammatory infiltrate within the vessel wall in Takayasu's arteritis is composed of $\gamma\delta$ -T cells, cytotoxic T cells, natural killer cells, T helper cells, and macrophages. Vascular endothelial cell injury in this disease is a result of either secretion of perforin by cytotoxic cells or Fas-Fas ligand-mediated apoptosis [13]. Increased production of proinflammatory IL-6 in the serum of patients' with Takayasu's arteritis and high serum level of regulated on activation, normal T cell expressed and secreted, a potent recruiter for mononuclear cells that comprise the inflammatory infiltrate, have also been noted [19]. An unknown antigen within the vasculature may trigger the inflammatory process. The T cell repertoire within the inflammatory infiltrate has been shown to be restricted, particularly among $\gamma\delta$ -T cells, suggesting selective antigen-driven T cell activation as part of disease pathogenesis. Interestingly, the literature points to colocalization of $\gamma\delta$ -T cells and both the mycobacterial heat shock protein-60/65 and the homologous human heat shock protein-60/65 within the inflammatory infiltrates in vessels in Takayasu's arteritis. Increased T cell reactivity to these antigens has also been demonstrated [20, 21]. Interestingly, in Crohn's disease, there is also evidence of increased T cell reactivity to mHSP65 [22].

Hospital course and therapeutic interventions

Preoperatively, the patient received 250 mg intravenous methylprednisolone for 3 days followed by intravenous cyclophosphamide at 500 mg/m². She did well postoperatively. Given the patient's desire to preserve fertility, cyclophosphamide was discontinued after 1 month. Mycophenolate mofetil starting at 1 g/day was added to her immunosuppressive regimen of infliximab at 10 mg/kg and high-dose steroids (20 mg Medrol daily). Three months later, her steroids had been tapered to 16 mg Medrol daily and her cardiac symptoms had resolved. A follow-up PET scan demonstrated resolution of inflammation in the large vessels with the exception of a small region of abnormal uptake within the carotid arteries.

Conclusions

In summary, we present a case of large-vessel granulomatous arteritis associated with an aortic arch aneurysm in a young woman with extraintestinal manifestations of Crohn's disease. The radiographic and pathological findings favored a diagnosis of Takayasu's arteritis. The occurrence of these two diseases in the same patient suggests a common pathogenesis, resulting in cell-mediated autoimmunity and granuloma formation.

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