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More than meets the eye

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Abstract

Rheumatologists take great pride in making elegant diagnoses. We carefully assess seemingly disparate signs and symptoms and use these clinical clues to make diagnoses based on predictable disease phenotypes. However, few clinical features of rheumatic disease are unique to a single disease process. Here we describe a case where the overlap of clinical features led to an initially broad differential diagnosis of seemingly unrelated diseases. Ultimately, the discovery of a radiographic finding allowed us to more clearly define the diagnosis, make inferences regarding the underlying pathophysiology, and intervene therapeutically with the goal of averting potentially significant morbidity.

CASE REPORT

A 27-year-old African American woman was admitted to the Johns Hopkins Hospital with fever and visual changes. She had been well until nine months earlier when she developed unilateral blurry vision in the left eye. The symptoms persisted, and she sought the care of an ophthalmologist. Examination at that time revealed bilateral acute anterior uveitis. She was treated with topical steroids and her vision returned to baseline.

Over the next few months, however, she developed debilitating fatigue and experienced an unintentional fifteen pound weight loss. One month prior to presentation, she noted the onset of daily low grade fevers and chills. On the day of admission, she developed a temperature of 103°F and a severe frontal headache. Her past medical history was notable for new-onset headaches that developed 18 months prior and were diagnosed as migraines. She worked as an engineer and had no history of alcohol, drug or tobacco use, or foreign travel. There was no family history of autoimmune disease. Review of systems was notable for the absence of Raynaud's, rash, chest pain, cough, shortness of breath, and change in mental status. She noted diffuse arthralgias of her hands and lower back, although she denied the presence of swollen joints.

On examination, the patient was a well-developed, well-nourished African-American woman. Although clearly uncomfortable, she was alert, fully oriented, and insightful. Temperature was 103°F. Blood pressure in the right arm was 97/62 mmHg; a blood pressure could not be measured in the left arm. Brachial and radial artery pulses were palpable and seemingly symmetric bilaterally. No carotid or subclavian bruits were auscultated. There were no oropharyngeal ulcers, and her conjunctivae were clear. Fundoscopic examination revealed normal optic discs without papilledema, retinal hemorrhages or exudates. Slit lamp examination revealed 1+ cell and flare in the anterior chambers in the right eye and 2+ in the left. Musculoskeletal exam revealed no synovitis or joint deformities. Nailfold capillary

microscopy was normal. Neurologic exam demonstrated preserved strength in all upper and lower extremity muscle groups with normal bulk and tone.

Laboratory data revealed a white-cell count of 3900 cells/mm³ with a normal differential, hemoglobin was 10.6 g/dL, hematocrit was 31.5%, and platelet count 245,000/mm³. Serum electrolyte levels, liver-function tests, complement levels and urinalysis were within normal limits. Total protein was 6.1 g/dL and albumin 3.1 g/dL. The erythrocyte sedimentation rate was elevated at 73 mm/hour and the C-reactive protein level was also high at 8.2 mg/dL. Lumbar puncture showed 2 WBC/hpf, 0 RBC/hpf, a normal protein at 19 mg/dL, and negative Gram stain and culture. Antinuclear, anti-double stranded DNA, and anti-neutrophilic cytoplasmic antibodies were all negative, as were HLA B27 antigen, rheumatoid factor, and RPR. ELISA for Lyme disease, HIV, hepatitis C, hepatitis B, and tuberculin skin testing were all unrevealing. Chest and lumbosacral spine X-rays were normal. Computed tomography (CT) of the head was negative. In the setting of this largely unrevealing work-up for an etiology of her uveitis and fever, CT imaging of the chest was obtained. Whereas no adenopathy or pulmonary infiltrates were seen, bilateral carotid arterial thickening was noted (Figure 1). Magnetic resonance imaging (MRI) confirmed the CT findings, revealing circumferential thickening of the aortic arch and great vessels without focal stenosis (Figure 2). These findings were diagnostic of aortitis.

DISCUSSION

This 27 year old woman, who initially presented with bilateral uveitis, proceeded to develop systemic inflammatory symptoms, persistent fevers, and ultimately a large vessel vasculitis. Were there any clues during her clinical course that could have predicted her ultimate diagnosis?

In a cohort of 1916 patients with uveitis, the most frequent systemic disease associations were the seronegative spondyloarthropathies (13.4%) (predominantly ankylosing spondylitis), sarcoidosis (4.5%), multiple sclerosis (3.1%), and Behcet's syndrome (1.8%). Indeed, systemic inflammatory disorders as a group were more common etiologies than infectious diseases, such as Lyme disease (12%) (1). Therefore, patients presenting with bilateral uveitis should be evaluated for the presence of systemic inflammatory processes, particularly in the context of arthritis and fever (2). These patients should be referred by the treating ophthalmologist to a rheumatologist for evaluation of a potential underlying immune-mediated multisystem rheumatic disorder (Figure 3) (3). However, our patient did not have any other localizing symptoms suggestive of a systemic process on her initial uveitis episode, contributing to the elusive nature of her underlying disease process.

When our patient re-presented with fever, arthralgias, unintentional weight loss and headache, CT imaging was appropriately pursued as part of the work-up for fever of unknown origin (FUO), yielding the discovery of aortitis and carotid arterial thickening. Importantly, the differential diagnosis for uveitis and concomitant aortitis narrows the differential diagnosis to a group of diseases (Table 1), which were considered in this case.

Lyme disease and tuberculosis as potential infectious etiologies were quickly ruled out with negative serology, normal cerebrospinal fluid, negative PPD, and lack of tick exposure or foreign travel. Syphilis was also considered unlikely in this case with a negative RPR; however, this spirochetal infection should be considered carefully in the context of uveitis and aortitis. Ocular findings occur in ~10% of patients with syphilis, among whom uveitis is the most common eye manifestation (4). Syphilitic uveitis is varied and can occur in the secondary or latent stage of the infection, involve the anterior or posterior segment of the uveal tract, and can be unilateral or bilateral (4). Syphilitic aortitis most frequently involves

the aortic arch and thoracic aorta and can lead to aortic rupture, aortic regurgitation, and heart failure (5). Although in 2000 the overall incidence of syphilis was the lowest it has been since 1941, it remains a significant public health concern today. The Centers for Disease Control report that between 2005 and 2006 the total number of syphilis cases in the United States increased by 11%, with the highest incidence of primary and secondary infection occurring among women age 20–24 years and in men 35–39 years of age (6). Hence, it is important to maintain a high index of suspicion for syphilis when a patient presents with multi-system inflammatory signs and symptoms, particularly the co-occurrence of uveitis and aortitis. In our case, the negative RPR and negative sexual exposure effectively ruled out this consideration.

Spondyloarthropathy was considered unlikely given the normal sacroiliac joint imaging and negative HLA B27 status. There were no oral or genital ulcerations to support a diagnosis of Behcet's syndrome, and her lumbar puncture results ruled out aseptic meningitis. Sarcoidosis, Crohn's disease, rhinogenic granulomatosis with necrotizing angitis (7) and Takayasu arteritis remained diagnostic considerations, given the rare reported associations of uveitis and aortitis in each of these granulomatous disease processes (8–14).

Several case reports and small case series describe the association of large vessel vasculitis with sarcoidosis (8). Uveitis is described in a number of these patients, who frequently present with ocular inflammation, then develop aortitis later in their course (8, 9). However, the lack of hilar adenopathy, pulmonary infiltrates, erythema nodosum, or inflammatory arthritis makes sarcoidosis an unlikely unifying diagnosis in this case.

Crohn's disease is an inflammatory granulomatous condition of the gastrointestinal tract characterized by transmural inflammation and fistula formation. Ocular complications of Crohn's, including conjunctivitis, blepharitis and uveitis are common; the latter occurring in ~5% of patients (10). In addition, vascular complications have been reported in 1.3% of patients with inflammatory bowel disease, with thromboembolic disease being most common (11). Notably, medium and large vessel vasculitis has also been described in patients with inflammatory bowel disease (11, 12). In several cohort studies of Takayasu arteritis, the reported frequency of associated Crohn's disease ranged from 3–9% (9, 12–14). In our case, the lack of GI symptoms, peripheral arthritis, or skin lesions made Crohn's disease unlikely. Genotyping for CARD15/NOD2 mutation, which confers susceptibility for inflammatory bowel disease, was not obtained in this case (15, 16). However, the inclusion of this test would be a reasonable diagnostic strategy in the evaluation of a patient with uveitis and gastrointestinal symptoms.

The ANCA-associated vasculitides encompass a number of distinct disorders, characterized by pulmonary capillaritis, glomerulonephritis, and inflammation of the sinonasal and upper respiratory passages. For example, rhinogenic granulomatosis with necrotizing angitis, in whom most patients are seropositive for c-ANCA and display high levels of anti-proteinase 3 antibodies, can also have profound ocular features, including uveitis (17, 18). Although aortitis is an uncommon feature of the ANCA-associated vasculitides, it has been reported both before and after the onset of more overt small vessel disease (19). Although several case reports have described concurrent ocular involvement (episcleritis, sclerokeratitis, conjunctivitis) and aortitis in the ANCA-associated vasculitides, none have described concurrent uveitis (19–22). However, our patient did not have any of the classic features to suggest a primary diagnosis of rhinogenic granulomatosis with necrotizing angitis, microscopic polyangiitis or the Churg-Strauss syndrome, including a lack of sinus or lung lesions, refractory asthma, abnormal renal function, eosinophilia or a positive ANCA serology (23).

Takayasu arteritis is a large vessel vasculitis in which the predominant feature and telltale sign is pulselessness. Pathologic studies and autopsy series revealed the presence of granulomatous inflammatory lesions in the media, adventitia, and throughout the vasa vasorum of the aorta and its main tributaries. This inflammation leads to intimal thickening, vessel stenosis, aneurysm formation, and vascular compromise. Despite its status as the prototypic large vessel vasculitis, Takayasu arteritis was originally described in the ophthalmology, and not the rheumatology, literature (24). Several more cases were subsequently described, after which the pathologic finding of panarteritis was first noted in 1940 (25). These early descriptions focused on the shared characteristics of fever, pulselessness, aneurysmal formation, and visual loss (25). Visual impairment was attributed to a lack of blood supply to the internal carotid artery resulting in low pressure flow to the retina, producing the arteriovenous anastomoses observed by Dr. Takayasu (25). Other forms of ocular pathology are also described in Takayasu arteritis, including reports of uveitis in pediatric and adult patients (Tables 2a + 2b) (9, 26–32). One such case is remarkably similar to the present report, occurring in a young African-American woman who initially presented with uveitis and four years later developed arthralgias, weight loss, elevated inflammatory markers and pulselessness (29).

In a retrospective cohort of 75 patients with Takayasu arteritis from the Cleveland Clinic, 12% presented with visual aberrations (blurring, scotoma, or diplopia). However, uveitis was not noted in this series (33). In a retrospective cohort of 45 patients in Ankara, Turkey from 1973 to 2003, 10% were reported as having visual symptoms including one patient with documented uveitis (26). In addition, among a cohort of 60 patients with Takayasu arteritis followed at the NIH from 1970 to 1990, there were two patients who presented with uveitis (9). The first patient developed unilateral anterior uveitis at the age of 4 and progressed 9 years later to have stenotic lesions of the aortic arch. This patient had a synovial biopsy of the wrist which showed noncaseating granulomas, interpreted as being indicative of sarcoidosis. A second patient developed bilateral uveitis and hilar adenopathy which on biopsy showed noncaseating granulomas. Angiography, however, showed extensive stenotic lesions consistent with a large vessel vasculitis. Both patients were African-American women (9).

In our case, we believe that the findings of bilateral uveitis, persistent fevers, elevated inflammatory markers, and asymmetric blood pressure are most consistent with a diagnosis of Takayasu arteritis. In retrospect, her adult-onset headaches in the preceding two years may have been an early symptom of the large vessel vasculitis. Headaches are described in 28–42% of patients with Takayasu arteritis (9, 13). As mentioned above, our patient did not have lymphadenopathy, diarrhea, hematochezia, malabsorption, glomerulonephritis or lung disease that would suggest the other above-mentioned granulomatous processes. We acknowledge the unusual finding of a left arm blood pressure that was unable to be auscultated in the presence of a preserved palpable brachial pulse. However, diffuse circumferential thickening of the aortic arch and left subclavian artery were noted on her initial MRI scan. Moreover, invasive hemodynamic pressure monitoring demonstrated a pressure gradient between the left and right upper extremities which might have accounted for this discrepancy. A unique feature of this case is the relatively short time interval between the development of uveitis and the notable discovery of aortitis, prior to the development of significant vascular stenosis or hemodynamic compromise. In previous case reports, the onset of uveitis was 2–9 years prior to the discovery of vascular abnormalities (pulselessness or significant stenoses) or occurred concomitantly with the onset of a significant vascular event (9, 29).

Imaging played a critical role in the diagnosis and long term follow-up of this patient. CT scan images revealed the initial diagnostic finding of carotid arterial thickening; however, in

the setting of an FUO, the utility of radiologic imaging to uncover the diagnosis of systemic vasculitis has been recently demonstrated (34). In one study of 67 such patients, a 31% increase in the diagnosis of systemic vasculitis was achieved by inclusion of MR imaging of the aorta and its major branches in the diagnostic algorithm (34).

Once the diagnosis of Takayasu arteritis was made, our patient responded quickly to therapy with steroids (1mg/kg/day dosing) and mycophenolate mofetil (MMF). MMF has demonstrated efficacy as a steroid-sparing agent in the management of both Takayasu arteritis and chronic uveitis (35–37). It was selected as our first-line agent as it does not adversely impact fertility or require dosing by assay of drug levels; overall, MMF has a favorable side effect profile. Other therapeutic options included consideration of azathioprine, methotrexate and cyclophosphamide. Our patient defervesced and had complete normalization of inflammatory markers within one week. Prednisone was tapered by approximately 10 mg per month; however, below a nadir dose of 10 mg daily, the patient experienced the return of systemic symptoms of malaise, arthralgias and corresponding increases in ESR and CRP levels. Given the inability to wean the steroid medication further, notwithstanding continued use MMF at a total daily dose of 3000 mg, the MMF was then switched to etanercept, an inhibitor of tumor necrosis factor alpha, with improved disease control (38, 39).

In summary, our patient demonstrates and underscores the interesting intersection of inflammatory ocular disease with the inflammatory vascular diseases in disorders with granulomatous infiltrates. Aortitis may be a challenging diagnosis to make, as with our patient, when systemic symptoms present before significant stenosis and resultant hemodynamic changes occur. A large vessel vasculitis could easily be overlooked on routine laboratory screening and radiologic evaluation, without a dedicated imaging study to assess for arterial wall edema, structural compromise and luminal narrowing. Each of the diseases considered in our patient, Takayasu arteritis, sarcoidosis, Crohn's disease, and rhinogenic granulomatosis with necrotizing angitis, seem very different at first glance. However, they share the overlapping features of aortitis and uveitis. The search for common pathophysiologic mechanisms among these diseases is an important and exciting area of ongoing investigation.

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Figure 1.
CT scan with IV contrast demonstrating marked bilateral circumferential thickening of the common carotid arteries (arrows).

Figure 2. Axial T1-weighted MRI with fat-suppression sequence demonstrates diffuse circumferential thickening of the aortic arch (arrows).

Figure 3.
Algorithm to identify an underlying etiology in the evaluation of uveitis. (Adapted from Reference 3)

Table 1

Differential Diagnosis for Co-Occurrence of Uveitis and Aortitis

<u>Infectious:</u>	<u>Vasculitis:</u>
Lyme disease	Bechet's syndrome
Syphilis	Takayasu arteritis
Tuberculosis	Wegener's granulomatosis
<u>Arthritis:</u>	<u>Other:</u>
Spondyloarthropathy	Crohn's disease
- Ankylosing spondylitis	Sarcoidosis

Table 2a
Case demographic and clinical features in published case reports of concurrent uveitis and Takayasu arteritis

Author	Age (years)	Gender	Race	Ocular finding	Vascular finding	Associated features	Treatment
Kausman et al (28)	10	M	Asian	Bilateral panuveitis	Vertebral+ subclavia stenoses	↑ESR, HTN, fever	CS + CYC followed by MTX
McDonald et al (32)	12	M	Asian	Bilateral uveitis	Renal artery, vertebral + subclavian stenoses	HTN	CS + CYC followed by MTX
Jolly et al (29)	22	F	AA	Bilateral uveitis	Carotid +subclavian stenoses	↑ESR	CS + MTX + infliximab
Becker et al (31)	5	F	AA	Unilateral anterior uveitis	Aortic arch dilatation; thoracic aorta stenosis	HTN	MTX + surgery
Kaliaperumal et al (30)	35	F	N/A	Unilateral hemorrhagic keratouveitis	Vertebral, carotid + subclavian stenoses	HTN	CS

M = male; F = female; AA = African-American; N/A = not available;
SC = subclavian; HTN = hypertension
CS = corticosteroids; CYC = cyclophosphamide; MTX = methotrexate

Table 2b

Cohorts of Takayasu arteritis reporting the frequency of uveitis as a disease feature

Author	Country	Size of cohort	Mean age (years)	Number (%) patients with uveitis
Soto et al (27)	Mexico	110	26	6 (5%)
Kerr et al (9)	USA	60	25 *	2 (3%)
Ureten et al (26)	Turkey	45	34	1 (2%)

* Median age reported.