Severe Hypertension With Large-Vessel Arteritis

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Small-vessel arteritis is associated with hypertension because the commonest varieties, granulomatous vasculitis with polyangitis and microscopic polyangitis with antineutrophil cytoplasmic autoantibodies, usually cause necrotizing glomerular disease. Medium vessel vasculitis, such as polyarteritis nodosa and Kawasaki disease, are less regularly associated with hypertension. Large-vessel vasculitis, such as giant cell arteritis, commonly coincides with hypertension. Takayasu arteritis, a granulomatous inflammation of the aorta and its major branches, generally afflicts patients aged younger than 50 years. Mikito Takayasu first described the condition in a woman reporting visual loss. Takayasu found abnormal anastomoses on funduscopic examination termed “coronary anastomosis” of the retinal vasculature because of the corona-like vessel connections. Katsutomo and Tsurukichi described similar young female patients and made the observation that the patients had absent radial pulses. Takayasu arteritis is rare in Western countries. The disease has been described worldwide with an incidence of up to 3.3 per million and is most common in Asia. However, Takayasu arteritis is by no means confined to Asians and, because of current mobility, clinicians must be aware of the disease. Watts et al inspected the United Kingdom General Practice Research Database. The overall annual incidence of Takayasu arteritis was 0.8 per million with a prevalence of 4.7 per million. The annual incidence in those aged younger than 40 years was 0.3 per million. In the Norfolk Vasculitis Registry population, 1 patient was identified (0.4/million/yr) with 3 prevalent cases (7.1/million). Onset at age 40 years or younger, claudication of an extremity, decreased brachial artery pulse, >10 mm Hg, difference in systolic blood pressure between arms, a bruit, and narrowing or occlusion of the aorta and its major branches are included in the American College of Rheumatology criteria. The presence of ≥3 of these 6 criteria demonstrated sensitivity of 91% and a specificity of 98%.3

Case

The patient is a 21-year-old woman with back pain and stiffness. Her symptoms progressed over the course of 1 year to include abdominal pain, paresthesias in both legs, and muscular weakness. She appeared in several emergency departments and underwent physical examinations and abdominal ultrasound studies. Nonsteroidal anti-inflammatory drugs were prescribed but nothing tangible was found. Her recorded blood pressures were elevated. Eight months later, a sudden severe headache followed by a grand mal seizure developed. Imaging disclosed a small subarachnoid hemorrhage and she was admitted to a neurosurgical service. No intracranial aneurysms were identified and her symptoms resolved with blood pressure-lowering drugs. No interventions were performed. Four months thereafter, she was admitted to another hospital because of back pain. At that admission, increased blood pressure, an abdominal bruit, anemia, and renal insufficiency were found. The hemoglobin was 5.6 g/dL, creatinine concentration was 2.2 mg/dL, and the erythrocyte sedimentation rate was 100 mm per hour. She was not iron-deficient and a bone marrow examination was consistent with anemia of chronic disease. She had only slight proteinuria, <1 g per 24 hours. A right kidney biopsy was performed and interpreted at another institution as showing nonspecific findings of “beginning” focal sclerosing glomerulosclerosis. Thereafter, MRI angiogram with gadolinium-based contrast material was performed revealing a tight concentric abdominal aortic constriction immediately above both renal arteries. Prednisone treatment for presumed Takayasu arteritis (age younger than 40 years, abdominal bruit, focal narrowing of the aorta) was initiated that was tapered to 20 mg/d. Her abdominal pain resolved. Several months thereafter, the patient was referred to us for further care.

We encountered an asymptomatic young woman born in Germany but of Turkish descent. Her medications were: prednisone 20 mg/d; lercanidipine 10 mg/d; doxazosin 4 mg/d; metoprolol 100 mg/d; cholecalciferol 400 IU/d; and calcium carbonate 600 mg with meals. Angiotensin-converting enzyme inhibitors were not included because these had resulted in an increase in creatinine concentrations. Her blood pressure was 130/70 mm Hg right, 130/60 mm Hg left, 120/60 mm Hg right leg, and 120/70 left leg mm Hg, respectively. The radial, femoral, and carotid pulses were all palpable. Visual acuity, funduscopic examination, chest, heart, and abdominal examinations were all unremarkable with the exception of a systolic bruit that was audible in the upper-mid abdomen. Neurologically, we detected no localizing findings, reflexes were symmetrical, and the sensory examination was normal. A chest roentgenogram and a 12-lead ECG were normal. The hemoglobin was 11.3 g/dL, leukocytes were 15 000/μL, C-reactive protein was 0.3 mg/
level of the right kidney and resolved at the level of the right renal pole. The narrowing was most pronounced at the orifice of the abdominal aorta that began above the level of the upper subclavian arteries, and a normal thoracic aorta. The upper abdominal aorta revealed aortic wall thickening of approximately 5 mm at the level of the celiac artery and an intensely constricted 4-mm diameter luminal area extending approximately 4 cm above the egress of the right renal artery (Figure 1A). The left renal artery could not be visualized and the left kidney was markedly contracted, whereas the right kidney was normal in size. The lower abdominal aorta, common iliac arteries, and femoral arteries were normal. Doppler ultrasound confirmed these findings. The left renal artery could not be identified with duplex Doppler and the right renal artery was found to be stenotic at its origin (not shown). The radiologist could not rule out compromise of the celiac and superior mesenteric arteries and the severe stenosis of the abdominal aorta that began above the level of the upper right renal pole. The narrowing was most pronounced at the level of the right kidney and resolved at the level of the right renal lower pole (Figure 1B). The right renal artery again revealed a tight stenosis at its origin. We next performed 18F-2-deoxyfluoro-D-glucose positron emission tomography to assess the disease activity (Figure 2). The study showed no evidence of hypermetabolism, suggesting a currently quiescent disease.

Clinically, we attributed the abdominal pain to compromise of the celiac and superior mesenteric arteries and the severe hypertension to renal artery stenosis in a solitary kidney. Although with medication the disease appeared quiescent and despite her current lack of symptoms, we were concerned that subsequent disease progression could result in dialysis-dependent renal failure, an additional intracerebral bleeding episode, or ischemic bowel disease. Our options were expectant management, interventional radiology, or vascular surgery. Our interventional radiologists had no experience in the management of Takayasu arteritis. The patient elected to undergo vascular repair at another institution.

The surgeon was unable to adequately clear the large amounts of inflammatory tissue to free the right renal artery and had to abandon plans for revascularizing the right kidney. Collateral blood flow around the celiac artery and superior mesenteric artery appeared adequate and therefore nothing was disturbed regarding these vessels. A large prosthetic conduit was implanted from the lower thoracic aorta to the lower abdominal aorta. Subsequently, she was again referred to our hospital. Her serum creatinine concentration was now 1.75 mg/dL.

We repeated the CT angiography. The superior aspect of the anastomosis between aorta and prosthesis (Figure 3A) and inferior anastomosis (Figure 3B) were visible. The right renal artery stenosis (Figure 3C) was identified. A computerized reconstruction (anterior view) showed the prosthetic graft running posterior to the spleen and left kidney (Figure 3D). The patient was discharged to outpatient care receiving metoprolol, clonidine, and hydrochlorothiazide. Her blood pressure was 140/80 mm Hg, her C-reactive protein was 0.3 mg/dL, and the serum creatinine concentration had decreased to 1.2 mg/dL. Her immunosuppressive regimen was prednisone 30 mg/d with plans for further reduction and methotrexate 10 mg/d with plans to further increase the drug to 20 mg/d.

**Discussion**

Our young patient confronts an uncertain future with a rare vascular disease that few physicians have encountered, severe resistant (3 antihypertensive medication classes) hypertension, a cerebral hemorrhage, and decreased renal function that could result in dialysis dependency. Similarly, her physicians face several management challenges. Takayasu arteritis can be arrested with immunosuppressive drugs. However, these drugs have substantial morbidity, particularly in young patients, and no information from randomized controlled trials is available. We had recommended surgery with the hope that bypass and renal revascularization would ensue. However, the renal revascularization could not be achieved and whether the bypass actually helped the patient clinically is not clear. An endovascular therapy with stent placement is clearly possible; however, the ideal timing for such an intervention is unclear in this currently asymptomatic patient with adequate but not normal renal function. Renal artery stenting is not without complications. We managed a woman earlier with renal artery stenosis who had an “in-stent” thrombosis after the intervention. Her kidney was eventually lost. Such a result would be, of course, catastrophic in the patient we present here.

Several large series of patients with Takayasu arteritis have been described. Vanoli et al examined 104 patients. They pointed out that the diagnosis was commonly delayed, with a mean of 16 months after onset of symptoms, which was similar to the delay in our patient. Most of their patients experienced nonspecific signs and symptoms indicative of an inflammatory disease in the early phase. Erythrocyte sedimentation rate appeared to predict disease activity. Almost all (93%) of their patients presented with vascular stenosis, followed by occlusion (57%), dilatation (16%), and aneurysm (7%). Half of their patients underwent an operation. The main
indications for intervention were renal vascular hypertension, cerebral hypoperfusion, and limb claudication. Glucocorticoids were the mainstay of treatment; however, treatment with cytotoxic agents was required in approximately half of the patients. Park et al. described 108 patients. They also found that a low erythrocyte sedimentation rate was a predictor of remission. A remarkably high erythrocyte sedimentation rate was initially present in our patient, similar to values encountered in patients with giant cell arteritis. Dagna et al. suggested that pentraxin-3 might be an ideal marker to monitor Takayasu arteritis and compared this marker to erythrocyte sedimentation rate and C-reactive protein in 57 patients monitored during treatment. They claimed that pentraxin-3 might be an ideal marker to monitor Takayasu arteritis and compared this marker to erythrocyte sedimentation rate and C-reactive protein in 57 patients monitored during treatment. They claimed that pentraxin-3 was a superior marker; however, confirmation would be necessary. Because C-reactive protein is a member of the pentraxin family, we did not pursue the matter further.

Mwipatayi et al. described 272 patients. The mean age at presentation was 25 years (range, 14–66 years) and 75% were women. Only 8% were white. Hypertension was present in 77% and was usually a consequence of renal artery stenosis or aortic coarctation. Heart failure was common. The entire aorta was involved in 70% of cases, as opposed to our patient who seems to have a localized involvement. Occlusions were noted in 93% and aneurysms were noted in 46%. Half of their patients underwent an operation with an operative mortality of 4%. Immunosuppression maintained disease control over 5 years, albeit in 30% of their patients. Most authors report the disease in older children or adults younger than 50 years of age. However, Takayasu arteritis can affect small children. Hijazi et al. reported 3 toddlers with Takayasu arteritis, aged 16 to 35 months. All exhibited extremely high blood pressures, ostensibly because of renal artery stenosis and absent pulses in some extremities. Also in the differential diagnosis is “middle aortic syndrome,” which is not necessarily a childhood disease but has been frequently diagnosed in children. Middle aortic syndrome may be acquired, caused by Takayasu arteritis, temporal arteritis, neurofibromatosis, fibromuscular dysplasia, retroperitoneal fibrosis, mucopolysaccharidosis, Williams syndrome, or congenital developmental anomaly in the fusion and maturation of the paired embryonic dorsal aortas. Segmental aortic stenosis may be located at the suprarenal, inter-renal, or infrarenal aorta, with a high propensity for concomitant stenoses in both the renal and visceral arteries. Hypertension proximal to the aortic stenosis and relative distal hypotension are characteristic findings in middle aortic syndrome.

Maksimowicz-McKinnon et al. observed that the prognosis is guarded in patients with Takayasu arteritis. In this cohort from the United States, the common manifestations at disease onset included loss or asymmetry of pulses (57%), limb blood pressure discrepancy (53%), and bruits (53%). Angiography revealed aortic abnormalities in 79% of patients and frequent involvement of the subclavian (65%) and carotid (43%) arteries. Almost all (93%) of their patients attained initial disease remission, but only 28% had a sustained remission of at least 6 months duration, particularly when prednisone was tapered to <10 mg daily. Both angioplasty and vascular surgery were initially successful, but recurrent stenosis occurred in 78% of angioplasty and 36% of bypass/reconstruction procedures. Thus, clinicians must anticipate recurrent disease, particularly with immunosuppressive drug reduction. Attempts to restore vascular patency are often initially successful, but restenosis occurs frequently. Chronic morbidity and disability occur in most patients.
Measuring blood pressure in Takayasu arteritis patients is not trivial. We measured blood pressure with conventional oscillometric sphygmometric techniques and detected $\approx 10$ mm Hg lower blood pressure in the legs than in the arms. The values should be higher in the legs than in the arms. We did not measure blood pressure directly and we did not assess central blood pressure or pulse-wave velocity. Both would have been of interest. Sohn et al$^{12}$ presented a 24-year-old woman who had a seizure and a left-side hemiparesis. Her blood pressure was an innocuous 113/70 mm Hg. Both femoral pulses were present. Her ECG exhibited voltage criteria for left ventricular hypertrophy and her heart was enlarged on chest roentgenogram. She had subtotal subclavian artery occlusion bilaterally and an aortic narrowing, similar to our patient. The stenosis masked a severe hypertension.

The pathogenesis of Takayasu arteritis is not clear and distinctly distinguishing this disease from the other more common large vessel arteritis is not easy. Giant cell arteritis and Takayasu arteritis have been considered distinct disorders based on their clinical features, age of onset, and ethnic distribution. However, on closer examination, these disorders appear more similar than different. The histopathology of arterial lesions in these diseases may be indistinguishable. Imaging studies have revealed large-vessel inflammation in at least 60% of patients with giant cell arteritis. Maksimonwicz-McKinnon et al$^{13}$ carefully compared these 2 conditions in 75 Takayasu arteritis patients and 69 patients with giant cell arteritis. Both conditions occurred predominantly in women (91% vs 82%) and non-blacks (88% vs 95%). More than half presented with headache (52% vs 70%). All Takayasu arteritis patients underwent imaging of large vessels, whereas only 69% of giant cell arteritis patients underwent such studies. However, three-quarters of those patients had at least 1 major arterial lesion. In both Takayasu arteritis and giant cell arteritis patients, the commonest site of involvement was the aorta (77% vs 65%) and subclavian arteries (65% vs 37%). Giant cell arteritis patients had more jaw claudication, blurred vision, diplopia, and blindness. The authors raised the interesting possibility that the 2 giant cell arteritides may represent a disease spectrum of a single disorder.

Conceivably, Takayasu arteritis is, in part, related to autoimmune mechanisms. Antiendothelial cell antibodies have been implicated.$^{14}$ A total of 9 antigens ranging in size from 18 kd to 200 kd on endothelial cells have been identified.$^{15}$ The antibodies induced increased expression of E-selectin and vascular cell adhesion molecule-1. They increased production of IL-4, IL-6, and IL-8. Sera from autoantibody-positive patients induced apoptosis of aortic endothelial cells. Cytokines have received substantial attention. Park et al$^{16}$ found that serum tumor necrosis factor-$\alpha$, IL-6, and IL-18 levels of patients with Takayasu arteritis were higher than those of controls, whereas interferon-$\gamma$ and IL-12 levels were not. However, Varma et al$^{17}$ specifically implicated IL-12 as an important mediator of inflammation in Takayasu arteritis. Matrix metalloproteinases have been suggested as novel disease markers. Matsuyama et al$^{18}$ identified matrix metalloproteinase-2 and claimed that matrix metalloproteinase-3 and matrix metalloproteinase-9 would be useful for determining disease activity. The investigated pathways implicated T-cell activation in the pathogenesis.

Chauhan et al$^{19}$ show that gamma/delta T-cells in patients with Takayasu arteritis are reactive to Hsp60 and exhibit cytotoxicity to aortic endothelial cells, suggesting a key role of Hsp60 and gamma/delta T-cells in the pathogenesis of the disease. Deng et al$^{20}$ examined the pathogenic pathways followed by T-cells in giant cell arteritis. If we accept the disease spectrum hypothesis,$^{13}$ then their results could be relevant to Takayasu arteritis. Deng et al found that plasma interferon-$\gamma$ and IL-17 and frequencies of interferon-$\gamma$-producing and IL-17-producing T-cells were markedly elevated in this condition. The findings have relevance to mechanisms determining T-cell fate in vasculitis. Pigott et al$^{21}$ pursued putative signaling pathways in giant cell arteritis focusing on infiltrating T-cell activation. The investigators found that immunohistochemical and gene expression analyses of giant cell arteritis-affected arteries revealed abundant NOTCH receptor expression and the ligands, Jagged1 and Delta1. Notch (named after the notched-wing phenotype in Drosophila) is a hetero-oligomer composed of a large extracellular portion, which associates in a calcium-dependent noncovalent interaction with a smaller piece of the notch protein composed of a short extracellular region, a single transmembrane pass, and a small intracellular region. The Notch protein sits like a trigger spanning the cell membrane, with part of it inside and part outside. Ligand proteins binding to the extracellular domain induce proteolytic cleavage and release of the intracellular domain, which enters the cell nucleus to modify gene expression. The authors devised 2 strategies to block NOTCH pathway activation. Their data showed that interfering with NOTCH signaling might be of therapeutic utility.

Both innate and adaptive immunity are pivotal in large-vessel arteritis. Pryshchep et al$^{22}$ found that medium and large arteries possess immune-sensing and T-cell stimulatory functions, whereby the vessels exhibit distinct Toll-like receptor profiles that support selective T-cell responses. The group further reported that vascular dendritic cells sense bacterial pathogens and regulate the patterning of the emerging arteritis. They were able to show that depending on the original danger signal, vascular dendritic cells edit the emerging immune response by differentially recruiting specialized T effector cells and direct the disease process toward distinct types of vasculitis.$^{23}$ The findings could implicate an external disease-initiating factor.

We elected a surgical option in the treatment of our patient. However, endovascular therapy has been applied with success.$^{24}$ Min et al$^{25}$ reported on 25 patients who were treated with angioplasty and stenting. They managed 58 vascular territories (7 aortic, 9 carotid, 3 vertebral, 11 subclavian, 2 superior mesenteric, 18 renal, 4 iliac, and 4 coronary arteries) that were treated with angioplasty only (19 lesions) or with stents (39 lesions). The authors point out that the treatments were performed after immunosuppressive therapy when the disease was relatively quiescent. The endovascular procedure was performed successfully in 52 (90%) of 58 lesions. During the mean 2-year follow-up, 9 (17%) treated segments restenosed; 4 were treated with repeat angioplasty. The overall
cumulative primary clinical success rate was 82%; secondary clinical success was 90%. Thus, an endovascular option remains open for our patient. Immunosuppressive agents including methotrexate, mycophenolate mofetil, and azathioprine added to corticosteroids are standard care for patients with Takayasu arteritis and generally achieve remission.\(^\text{26,27}\)

Unfortunately, as our patient also illustrates, relapse is common when prednisone is tapered to dosages of 15 mg/d or less.

**Perspectives**

Our patient had typical course of Takayasu arteritis, a rare but important form of large-vessel arteritis. Therapeutic successes must address both the inflammatory and the myointimal proliferative components of Takayasu arteritis. New drugs that target intimal hyperplasia and drug-eluting stents could improve therapeutic outcomes in this condition.

**Disclosures**

None.

**References**

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