Collateral Damage: A Differential of Takayasu Retinopathy

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Abstract

Background: Takayasu retinopathy is the ocular manifestation of Takayasu arteritis, a vasculitis affecting the aorta and aortic branches. Ocular manifestations are a result of cerebral and ophthalmic nonperfusion, and are noted in 8.1% to 68% of patients with Takayasu arteritis. Management of Takayasu retinopathy relies on treatment of the underlying systemic condition.

Case Report: A 60 year old African American male was referred for a comprehensive eye exam after abnormal findings were noted on his diabetic teleretinal exam. Upon clinical examination, the patient was diagnosed with moderate to severe diabetic retinopathy, and a fluorescein angiography was ordered due to the presence of irregular vessels on the optic nerves. Takayasu retinopathy was considered as a differential diagnosis after review of the fluorescein angiography. Further work up with magnetic resonance angiography (MRA) showed no signs of significant stenosis.

Conclusion: Takayasu retinopathy is a rare ocular manifestation that can aid in diagnosing a rare and previously undetected systemic disease of Takayasu arteritis. It is important for primary eye care providers to be assertive in performing additional diagnostic tests to prevent misdiagnosis and management of an underlying systemic condition. Keywords: Takayasu arteritis, Takayasu retinopathy

Introduction

Takayasu arteritis is a rare autoimmune disease that was first described in 1761 by Giovanni Battista Morgagni. Takayasu retinopathy, however, was not known until 1908 when Dr. Mikito Takayasu, an ophthalmologist in Japan, documented wreath-like blood vessels radiating from the optic nerve in one of his patients. Known as the “pulseless disease” due to its characteristic sign of an absent or faint pulse, Takayasu arteritis has a prevalence of 0.4-2.6 cases per million, with a strong predominance in females (82.9-97.0%). A broad range of 8.1% to 68% of these cases have ocular manifestations known as Takayasu retinopathy.

At the comprehensive eye exam, two months after the diabetic teleretinal exam, the patient’s best corrected visual acuity was 20/20 in both eyes. Pupils, extraocular movement, and intraocular pressures were within normal limits. Anterior segment evaluation was unremarkable. On dilated fundus exam, the cup to disc ratio was 0.50 round in the right eye and 0.45 round in the left eye. Abnormal vessels were noted along the optic nerve disc margins in both eyes. The posterior pole exhibited multiple blot hemorrhages and IRMAs along the superior and inferior arcades of both eyes (Fig. 1). The patient was diagnosed with severe NPDR in the right eye and moderate NPDR in the left eye, as well as stage 2 hypertensive retinopathy. Due to the abnormality of the vessels radiating from the optic nerves, a fluorescein angiography was ordered for further evaluation.
Fluorescein angiography revealed lacey non-leaking vessels surrounding the optic nerves with multiple microaneurysms in the periphery. Areas of non-perfusion were also noted in the periphery without signs of neovascularization (Fig. 2). Given the pattern of collateral vessels and microaneurysms, Takayasu retinopathy was considered. An MRA of the head and neck without contrast was subsequently ordered, and the results showed no significant stenosis. There was no indication of large vessel vasculitis, including gross vascular beading, or alternating areas of stenosis and dilation. The overall collected data concluded that the patient had severe non-proliferative diabetic retinopathy, however the differential of Takayasu retinopathy is an interesting and mostly unknown retinopathy that evokes further discourse.

Discussion
Epidemiology
The prevalence of Takayasu arteritis differs slightly between countries, with the majority of cases reported in Japan. An exception to female predilection is observed in India, where males have stronger association with the disease. Takayasu arteritis tends to manifest at a young age, between the second to third decade of life, although 13.0% to 17.5% of patients are diagnosed after 40 years old. Even so, a delay in diagnosis is four times higher in younger individuals compared to adults. Independent factors that delay the diagnosis of Takayasu arteritis include age less than 15 years old and erythrocyte sedimentation rate (ESR) less than 30 mm/hour. There is some speculation that Takayasu arteritis is part of a more commonly known disease: giant cell arteritis.

Signs/Symptoms
The systemic symptoms of Takayasu arteritis are rather non-specific and can include fever, malaise, weight loss, headache, and angina. As the disease progresses, pain in the extremities, limb claudication, bruit, absent pulse, loss of blood pressure, syncope, hemiplegia, or stroke can develop. Claudication and dizziness are the most common symptoms of the disease. Ocular symptoms are also vague and includes amaurosis fugax, visual disturbances, subjective reduction in vision, or patients may be asymptomatic. Approximately 25.7% of patients with Takayasu arteritis experiences amaurosis fugax. As the disease advances, a decrease in intraocular pressure may also be noted. Patients with severe stenosis can experience worsening of vision when in upright position due to reduced cerebral hypoperfusion. These broad symptoms illustrate why the disease is difficult to diagnose.

Presentation/Risk Factors
Systemically, Takayasu arteritis presents as an attenuation of the aorta and aortic branches due to inflammation of the arteries. The artery most commonly affected is the aorta, followed by the subclavian, common carotid, and renal artery. On CT angiography, the most commonly affected segment of the aorta is the abdominal aorta, followed by the descending aorta, the ascending aorta, and the arch. For arterial branches,
the left carotid artery is the most frequently affected, followed by the left subclavian artery, right common carotid artery, and the right subclavian artery.7 Another notable characteristic of the disease is that patients will seem to lack a pulse. There may be vastly different blood pressure readings between two different limbs, or the blood pressure reading may even be unreadable.3 In regard to lab testing, elevated ESR and CRP have also been noted.12

No correlation has been found between the duration of Takayasu arteritis and the severity of Takayasu retinopathy.1 Takayasu retinopathy can be categorized into four different stages.19 Initially stage 1 presents with distension of the veins, stage 2 displays microaneurysm formation, stage 3 shows arteriovenous anastomosis formation, and finally stage 4 shows ischemic complications.13 Visual acuity tends to be unaffected during the first three stages due to preservation of macular function.14 One of the hallmark signs of Takayasu retinopathy is the development of wreath-like collateral vessels around the optic disc during stage.3,14

Takayasu arteritis is mainly seen in the female population, with one study reporting a 6.6:1 female to male ratio.15 While this disease is most prominent in Asian patients, Caucasian patients have a greater mortality rate.15 There may be a genetic risk factor for Takayasu arteritis with the gene HLA-B*52 impacting the severity of the disease.6 Co-morbidities most commonly seen in patients with Takayasu arteritis include hypertension, diabetes mellitus, dyslipidemia, and heart failure.7 Cerebrovascular attacks can occur as the first presenting sign in young patients.7

Etiology/Pathogenesis
Takayasu arteritis is an autoimmune disease that causes panarteritis with acute granulomatous, chronic, and exudative inflammation.14 Inflammatory cytokines such as interleukin-6 (IL-6) and matrix metalloproteinase (MMP) are upregulated in these patients leading to further progression of Takayasu arteritis.16 Inflammatory lesions along the arterial wall become diffuse and fibrotic.8 The majority of these lesions are stenotic, while a third of the lesions are aneurysms. The stenosis of the descending aortic arch may cause irregularity in blood pressure in different limbs.14 Narrowing of the lumen causes attenuation of the aortic arch which can lead to cerebral and ocular ischemia.14 The ocular ischemia may then develop into Takayasu retinopathy.

Differential Diagnoses
When considering if a patient has Takayasu arteritis, it is important to also consider other vasculitides, and in particular giant cell arteritis. Both diseases are predominantly seen in females, with a similar pattern of arterial lesions and similar histopathology.3 It is theorized that Takayasu arteritis and giant cell arteritis are both on the spectrum of the same disease.3 However, one main differentiating factor is that Takayasu arteritis tends to affect a younger population in their second to third decade while giant cell arteritis affects an older population in the sixth to ninth decade of life.3 Giant cell arteritis is uncommon in African, Arabic, or Asian countries, while Takayasu arteritis is most prominent in Asia.17 Takayasu arteritis has a much greater prevalence in women compared to giant cell arteritis (90% vs 50-75% respectively).17 In regards to lab work, ESR and CRP are increased in over 95% of cases of giant cell arteritis.17 Elevated ESR is only 36% sensitive and 83% specific for Takayasu arteritis.18 Takayasu arteritis affects a much wider spread of vascular territories than giant cell arteritis, making Takayasu arteritis more difficult to diagnose.19 Occlusive arterial lesions are more common in Takayasu arteritis while aneurysmal findings are characteristic of giant cell arteritis (table 1).19

<table>
<thead>
<tr>
<th>Takayasu Arteritis</th>
<th>Giant Cell Arteritis</th>
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<tr>
<td>Presents 2nd to 3rd decade of life</td>
<td>Presents 6th to 9th decade of life</td>
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<tr>
<td>90% of cases are in women</td>
<td>50-75% of cases are in women</td>
</tr>
<tr>
<td>Most common in Asian countries</td>
<td>Rare in African, Arabic, and Asian countries</td>
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<tr>
<td>Normal ESR and CRP</td>
<td>Elevated ESR and CRP</td>
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Table 1: Comparison of distinguishable characteristics between Takayasu arteritis and giant cell arteritis

There are multiple differential diagnoses that should be kept in mind when considering Takayasu retinopathy. In the case of the patient presented above, diabetic retinopathy was the main differential due to the presence of microaneurysms that may be noted with both diabetic retinopathy and Takayasu retinopathy.

If a diagnosis of Takayasu arteritis has already been made and ocular findings are present, ocular ischemic syndrome, anterior ischemic optic neuropathy, and hypertensive retinopathy should also be considered as these conditions are possible complications of Takayasu arteritis.1 Hypertensive retinopathy may be noted when Takayasu arteritis affects the renal artery leading to severe hypertension.20 While these diseases can present concurrently with Takayasu retinopathy, it is uncommon.1

Diagnostic Testing
The gold standard for diagnostic testing for Takayasu arteritis is digital subtraction angiography (DSA).6 However, this imaging technique is invasive and exposes the patient to contrast media.6 DSA may miss minor lesions as it images the lumen rather than the vessel wall.6 Safer, non-invasive tests that are more commonly used for diagnosis are MRA, carotid Doppler ultrasound (CDU), computerized tomography angiography (CTA), and positron emission tomography (PET) with 18F-fluorodeoxyglucose.6 Both MRA and CTA have a specificity of 100% and a sensitivity of greater than 90% in detecting Takayasu arteritis.21 An advantage to MRA, CDU, and CTA is that both the lumen and the vessel wall are imaged.
allowing identification of both early and late complications of Takayasu arteritis. CTA should not be used for follow up assessment due to repeated patient exposure to radiation. PET on the other hand, can measure inflammatory cells in the vessels, but it is non-specific which may make it difficult to differentiate between other vasculitis disease.

Imaging is also essential in diagnosing Takayasu retinopathy and fluorescein angiography (FA) is considered the gold standard. Characteristic FA findings with Takayasu retinopathy include delayed artery to retina circulation time and microaneurysms. Other findings include arteriovenous shunts, arterial or venous occlusions, and venous dilatation. Peripheral choroidal nonperfusion and delayed arteriovenous filling time is seen in more severe cases of the disease.

Optical coherence tomography angiography (OCTA) may also aid in the diagnosis of Takayasu retinopathy. OCTA typically reveals an enlarged foveal avascular zone at the superficial choroidal plexus (SCP) along with perifoveal anastomotic capillary arcade rupture, and microaneurysms and vascular loops at the SCP.

**Diagnostic Criteria**

There are two sets of diagnostic criteria for Takayasu arteritis; one by the American College of Rheumatology (ACR) and another modified version of Ishikawa's diagnostic criterion by Sharma et al. Comparing the two criteria, the ACR has 90.5% sensitivity and 97.8% specificity. The modified Ishikawa diagnostic criterion, on the other hand, has a 92.5% sensitivity and 95% specificity. The modified Ishikawa's criteria is the most updated criteria for the disease and takes into account an improved understanding of the disease. The three major criteria for diagnosis of Takayasu arteritis are left mid subclavian artery lesion, right mid subclavian artery lesion, and characteristic signs or symptoms lasting for at least one month. The minor criteria include elevated ESR, carotid artery tenderness, hypertension, aortic regurgitation or annuloaortic ectasia, pulmonary artery lesion, left mid common carotid lesion, distal brachiocephalic trunk lesion, descending thoracic aorta lesion, abdominal aorta lesion, and coronary artery lesion. A high probability of Takayasu arteritis is indicated if the patient exhibits at least two major criteria or one major and two minor criteria.

**Management**

Management of Takayasu retinopathy is accomplished by management of the underlying disease of Takayasu arteritis. The first line of treatment is high dose corticosteroids, typically 1mg/kg/day of prednisolone. While there is a positive benefit to this treatment, relapses may occur while tapering the steroid dosage. Immunosuppressive agents like methotrexate, azathioprine, and cyclophosphamide have also been prescribed for this disease.

Immunosuppressive agents in combination with corticosteroids effectively manage the disease in 92.8% of patients and increase the time period between relapse. The use of corticosteroids and immunosuppressive agents may also increase the chance of infection in these patients.

Due to elevated levels of tumor necrosis factor-alpha (TNF-α) seen in patients with Takayasu arteritis compared to healthy patients, studies have tested the use of anti-TNF agents such as infliximab on patients where the previous two treatments were ineffective. Although most study sizes were small due to the rarity of the disease, some positive effect in helping patients discontinue corticosteroid treatment has been demonstrated, and anti-TNF agents are considered the third line of treatment. Patients on infliximab showed 70 to 90% remission of the disease and 40% of those patients were able to discontinue glucocorticoids. Adding infliximab as an adjunct to immunosuppressive agents has also shown better control of Takayasu arteritis in patients compared to treatment with immunosuppressive agents alone.

Considered the fourth line of treatment for this disease, tocilizumab blocks the pro-inflammatory cytokine IL-6. Similar to TNF-α, IL-6 levels have been shown to be elevated in patients with Takayasu arteritis. In small studies, tocilizumab has been shown to have similar effectivity to anti TNF-α agents, with 80% showing improvement in 3 months and less than 20% experiencing a relapse. However, incidence in relapses were shown to increase after discontinuation of treatment, therefore tocilizumab is not considered curative. In comparison with cyclophosphamide, tocilizumab had better success in vascular inflammation reduction and greater effectiveness in reducing IL-6 and MMP-9 cytokines.

For patients with chronic Takayasu arteritis, more invasive intervention should be considered such as balloon angioplasty, stent, and stent graft replacement. Surgery is indicated when there is cerebrovascular or coronary artery ischemia, claudication in the extremities, or severe renal artery stenosis. In a paper published by Sanchez-Alvarez et al, surgical intervention was required in 43.9% of patients with Takayasu arteritis. Surgical management should only be attempted after inflammation suppression of the vessel walls. Stent grafts, used to reduce luminal blood flow and thereby decreasing chronic inflammation, reduce the occurrence of restenosis compared to older techniques like percutaneous transluminal angioplasty. Complications from surgery include restenosis, thrombosis, cerebrovascular accident, arterial dissection, and bleeding. For patients with severe disease, surgical treatment can increase survival rate to 73.5% at 20 years. Percutaneous angioplasty and stenting of aortic arch vessels has shown to cause regression of Takayasu retinopathy especially if neovascularization has yet to develop. If the cause of reduced acuity is from hypoperfusion, endovascular revascularization may reverse vision loss. Managing the ocular complications of Takayasu arteritis are done by performing panretinal photocoagulation to reduce the development of neovascularization secondary to retinal ischemia.
Patients with Takayasu arteritis have a 2.7 times increase in mortality compared to their healthy counterparts. Seventy four percent of patients report difficulty performing activities of daily living, and 23-47% of those reported being fully disabled. These patients have increased susceptibility to heart failure, strokes, myocardial infarctions, and transient ischemic attacks, which significantly increases mortality. Strokes occur in 8.9% to 12% of patients that have Takayasu arteritis, and 3.4% experience myocardial infarctions. A strong risk factor for increased morbidity is the presence of aortic valve regurgitation. Congestive heart failure is the leading cause of death in these patients.

The relapse rate of Takayasu arteritis is 50%. Male gender, elevated CRP levels, and carotidynia independently increase the relapse rate two fold. One study reported that disease activity can be predicted by "thickened arterial wall with mural enhancement and an attenuated ring on delayed phase images" on CT angiography. Congestive heart failure has been shown to be the main cause of death in 50% of patients with Takayasu arteritis. Retinopathy increases the chance of vascular complication by 3.4 fold. Even so, prognosis has improved thanks to early diagnosis, more sophisticated imaging techniques, and advanced medical therapy.

Complications
The most common complication of Takayasu arteritis is hypertension, presenting in 50% to 75% of patients. Approximately 13-25% of patients with Takayasu arteritis develop aortic valve regurgitation, which is suspected in causing retinal hypoperfusion in early stages of Takayasu retinopathy. As a result of vascular damage, neurological manifestations occur in up to 50% of patients.

Ocular complications for Takayasu retinopathy typically do not occur until stage 4. Progression from stage 3 to stage 4 can take years to occur. It takes approximately two years for the peripheral retina to become nonperfused after arteriovenous shunts are formed. At this point visual acuity can become affected. Nonperfusion of the retina can lead to sight threatening changes such as neovascular glaucoma, vitreous hemorrhages, fibrovascular membranes, and tractional retinal detachments. Besides Takayasu retinopathy, development of ocular ischemic syndrome and anterior ischemic optic neuropathy has also been connected with Takayasu arteritis. Treatment of Takayasu arteritis can also lead to ocular complications. The initial standard of treatment for the disease is corticosteroids which may cause steroid induced cataracts as well as glaucoma. Although quite rare, there have been cases with small vessel involvement in patients with Takayasu arteritis. Small vessel involvement, including retinal vessels, may lead to a retinal vein or artery occlusion.

Conclusion
Takayasu retinopathy is the ocular manifestation of a rare systemic disease. While this disease holds similarities to other more common ocular conditions, certain characteristics such as wreath-like collaterals at the optic nerve are unique and warrant further testing to determine if there is underlying systemic disease.

References


