Acute Limb Ischemia in Cogan Syndrome

Michael M. Mohseni

Corresponding Author: Michael M. Mohseni, e-mail: mohseni.michael@mayo.edu
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Patient: Male, 50-year-old
Final Diagnosis: Cogan’s Syndrome • vascular ischemia • vasculitis
Symptoms: Change in extremity temperature • extremity pain • pulselessness
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine • Rheumatology

Objective: Rare disease
Background: Cogan syndrome is a rare autoimmune disorder associated most frequently with ocular, vestibular, and auditory involvement from presumed small vessel vasculitis. Cogan syndrome, in a significant proportion of patients, can progress to systemic symptoms, including gastrointestinal, neurologic, and musculoskeletal manifestations. Large-vessel involvement has also been described in some cases (eg, aortitis), but acute limb ischemia in the setting of this illness has been infrequently reported.

Case Report: We present a rare case of Cogan syndrome complicated by acute vascular ischemia of the left upper extremity. A 50-year-old man presented with symptoms of severe acute pain and weakness of the left arm. The patient endorsed a diagnosis of Cogan syndrome 4 years prior in the setting of unilateral left-sided hearing loss and bilateral uveitis. A physical examination revealed pallor of the left forearm and pulselessness at the wrist. Computed tomography angiography was suggestive of vasculitis and concerns for embolic occlusion of several arterial structures of the left upper limb. After consultation with various specialists, the patient was treated with high-dose steroids, anticoagulants, and topical nitroglycerin and experienced significant clinical improvement.

Conclusions: Treatment of Cogan syndrome with severe systemic manifestations depends on the organ involvement and degree of extension. Our patient’s presentation serves as an impressive example of systemic vasculitis with subsequent acute ischemia in the setting of this rare autoimmune disorder. In such a case, given the potential for life- or limb-threatening systemic vascular catastrophes, emergent interventions (including imaging, anticoagulation, and specialist involvement) are required to prevent untoward outcomes.

Keywords: Cogan Syndrome • Ischemia • Vasculitis
Background

Cogan syndrome (CS) is a rare autoimmune disorder, with approximately 300 cases reported in the current literature [1]. Although patients can present at any age, this disease is most frequently seen in younger adults from 30 to 40 years of age [1]. It is associated most frequently with ocular, vestibular, and auditory involvement from presumed small-vessel vasculitis. Clinical manifestations include tinnitus, vertigo, hearing loss similar to Meniere’s disease, but these occur in conjunction with ocular symptoms of interstitial keratitis, such as eye redness, sensitivity, and blurred vision [2,3]. CS is considered “typical” if ocular and vestibuloluditory symptoms occur within 2 years of presentation, and “atypical” if greater than 2 years elapse between these 2 organ systems’ dysfunction.

Vogt-Koyanagi-Harada syndrome (uveitis, alopecia, poliosis, plus vitiiligo), Susac syndrome (retinocochleocerebral vasculopathy), and congenital syphilis are possible differential diagnostic considerations for CS [2]. Various autoimmune diseases, however, have also been implicated in a minority (8-10%) of patients with CS, including Wegener’s granulomatosis, sarcoidosis, Takayasu arteritis, polyarteritis nodosa, rheumatoid arthritis, and inflammatory bowel disease [1]. Large vessel vasculitis, specifically aortitis, has been observed in up to 10% of patients with CS [1], but acute limb ischemia in the setting of this illness has been reported in only a few case reports. Treatment of patients presenting with serious systemic vasculitis typically requires a multi-disciplinary approach with considerations for medical therapies; aortic valve replacement, for example, has been described in severe aortitis and aortic insufficiency [4]. We present a rare case of CS complicated by acute vascular ischemia of the left upper extremity.

Case Report

A 50-year-old man presented to the Emergency Department (ED) with concerns of numbness, tingling, and severe pain in his left upper extremity over the previous 24 h. The pain was predominantly in the forearm and hand. He noticed a dusky discoloration to the left hand and crescendo pain, which prompted an ED visit. The patient denied fevers, chills, rash, headache, chest pain, shortness of breath, and peripheral edema. The patient did endorse a medical history significant for CS, which was diagnosed 4 years prior at an outside facility in the setting of unilateral left-sided seno-neural hearing loss, followed shortly thereafter by bilateral anterior uveitis. This initial presentation was associated with markedly elevated inflammatory markers (C-reactive protein, 228 mg/L). Per outside records, the patient was treated initially with rituximab, with the addition of azathioprine as a steroid-sparing agent several months later. However, after a flare of disease approximately 1 year later, with fatigue, tinnitus, photophobia, uveitis, and sudden right-sided hearing loss, azathioprine was held and prednisone 60 mg orally (PO) daily was started. The patient had continued progressive hearing loss and was evaluated 2 years into his illness at a quaternary care facility, where a more unifying diagnosis of CS was made. His condition subsequently progressed to inflammatory arthritis of several major joints and severe bilateral hearing loss. Although no frank episodes of vasculitis were reported in his prior history, the patient did have 1 episode of pyoderma gangrenosum requiring escalating doses of immunosuppressants. He currently denied any new symptoms on this ED visit related to hearing loss, uveitis, or arthritis. His up-to-date medications included adalimumab 40 mg subcutaneously every 2 weeks, mycophenolate 2000 mg PO daily, atorvastatin 20 mg PO daily, and prednisone 10 mg PO daily (maintenance dosing).

Upon arrival to the ED, the physical examination was concerning for pallor and coolness to the left upper extremity extending from the forearm into the hand. The range of motion was limited, secondary to severe pain. Wrist pulses were not palpable, but a bedside Doppler ultrasound revealed weak brachial and radial artery pulses. An initial laboratory evaluation was significant for a mild elevation of inflammatory markers (sedimentation rate of 30 mm/h, C-reactive protein of 32.5 mg/L).

Figure 1. Computed tomography angiography (maximum intensity projection) of the left upper extremity taken at time of presentation, showing multiple areas of occlusion and findings consistent with vasculitis. Complete occlusion of a 4.5-cm segment of the left subclavian artery at the level of the clavicle (arrowheads) is present with re-opacification distally from collaterals. Another 2.5-cm segmental occlusion is evident involving the distal brachial, proximal radial, and proximal ulnar arteries at the level of the bifurcation (single arrow) with re-opacification of the radial and ulnar arteries by collaterals surrounding the elbow. Finally, there is an 8.1-cm segmental occlusion of the ulnar artery extending from the mid-forearm to the level of the wrist (double arrow) with re-opacification of the ulnar artery more distally near the level of the wrist.
Computed tomography angiography of the left upper extremity was performed, showing multiple areas of embolic occlusion and findings consistent with vasculitis (Figure 1). Specifically, the left subclavian artery showed wall thickening with stenosis and occlusion at the level of the clavicle. Multifocal arterial occlusions consistent with emboli were also noted involving the bifurcation of the brachial artery, proximal radial artery, and mid-to-distal ulnar artery. There was distal re-opacification of the radial and ulnar arteries by collateral vessels. On further workup in the hospital, the patient was noted to have a weakly positive antiphospholipid cardioliqin IgM antibody of 22.7 MPL (negative <15.0 MPL), but this did not meet diagnostic criteria for antiphospholipid antibody syndrome. Additional rheumatologic and oncologic workup was unrevealing, including negative rheumatoid factor, centromere antibodies, hepatitis C virus antibodies, beta-2 microglobulin, antinuclear antibodies, ANCA, and cryoglobulins.

The Vascular Surgery Department was consulted emergently in the ED. Given the concern that the primary underlying process was autoimmune and vasculitis-mediated, no acute surgical interventions were indicated. Recommendations included consultation with the Rheumatology Department, continuous high-intensity heparin drip intravenously, vascular mittens, topical 2% nitroglycerin to the left upper extremity, and pain control. On admission, a rheumatologist evaluated the patient and agreed that the presentation was concerning for worsening chronic vasculitis, suggesting the possibility of an acute thrombotic or embolic event. The addition of intravenous methylprednisolone 1000 mg daily for 3 days was suggested and initiated. The patient was maintained on his previous immunosuppressants as well, with the exception of the oral prednisone. Additional consultation was obtained with the Hematology Department to determine the optimal anticoagulation regimen in this setting. Continued parenteral anticoagulation with heparin was recommended until there was clinical improvement, and then bridging to oral warfarin monotherapy (1 mg daily) was recommended, with an INR goal of 2 to 3. A transesophageal echocardiogram revealed there was no cardiac thrombus as a potential source of his limb ischemia.

The patient improved significantly with these therapies over the course of 5 days. He regained distal left upper extremity pulses, perfusion improved, and his pain subsided. He was discharged on oral warfarin therapy (1 mg daily), with an INR of 3.0 upon release from the hospital, along with a prolonged oral high-dose prednisone steroid taper (60 mg total for 10 days, 55 mg for 14 days, 50 mg total for 14 days, 45 mg daily for 14 days, 40 mg for 14 days, 35 mg for 14 days, 30 mg total daily for 14 days). He was also continued on his previous dosing of adalimumab 40 mg subcutaneously every 2 weeks and mycophenolate 2000 mg PO daily. In a 2-month follow-up with an outside rheumatologist, the patient noted no further left upper extremity pain or symptoms. Furthermore, the patient had no new vasculitic lesions on computed tomography angiography of the chest, abdomen, and pelvis. The patient’s only noted medication change was the addition of tocilizumab 162 mg subcutaneously weekly and discontinuation of the adalimumab.

**Discussion**

We describe a case of a patient with CS presenting with acute limb-threatening vasculitis. Although our patient was diagnosed with CS after typical oculovestibular symptoms of uveitis and hearing loss, he had already progressed to have systemic illness in the form of inflammatory arthritis. Reports of systemic manifestations in CS vary but can be as high as 66% to 80% of patients [1,3]. Cardiovascular, neurologic, and gastrointestinal involvement have all been reported in such cases. Aortitis is the primary large-vessel involvement in severe systemic cardiovascular CS cases. The ascending aorta, aortic valve, and even coronary arteries can be involved, and in up to 50% of these cases, aortic valve replacement is required because of severe valvular insufficiency [3,5]. Even less frequently described are cases of limb vascular ischemia, claudication, and necrosis [6]. The exact incidence, however, of acute ischemia in CS remains unknown. In these patients, arteriography can reveal embolic or thrombotic phenomena in the background of profound arterial stenosis, as was observed in our patient. Given our patient’s underlying CS, lifelong anticoagulation would also be required [7].

Although not classified as a true vasculitis phenomena, pyoderma gangrenosum has been reported in a handful of cases of CS, similar to that seen in our patient’s reported history [8]. Regarding the systemic arthritis seen in our patient, 1 large case series reported arthritis as systemic disease in 23% of patients with CS [9]. Furthermore, arteritis complications in CS can develop many years after the initial diagnosis, even if the disease seems quiescent [10]. It is unclear in our patient’s case why a worsening systemic flare may have developed despite his taking multiple immunosuppressants, but he appeared to be in the minority of CS individuals, with severe progressive disease from time of onset of diagnosis, thus highlighting the important nature of this case.

Treatment of CS with severe systemic manifestations depends on the organ involvement and degree of extension. In our case, vascular surgery, hematology/oncology, and rheumatology teams were involved early in the patient’s care because of the need for multiple simultaneous therapies, including steroids, cytotoxic agents, and anticoagulants. For patients with CS who improve on high-dose steroid therapy, a prolonged taper over a period of 2 to 6 months may be required to prevent the rebound of symptoms [10].
Conclusions

Our patient’s presentation serves as an impressive example of systemic vasculitis subsequently causing acute vascular ischemia in the setting of CS, a rare autoimmune disorder typically associated with oculovestibular symptoms. Unfortunately, since CS is a highly uncommon disorder, the exact incidence of limb ischemia in severe disease remains unknown. In our case, given the potential for life- or limb-threatening systemic vascular catastrophe, emergent interventions (including imaging, anticoagulation, and specialist involvement) were required to prevent untoward outcomes.

Declaration of Figures’ Authenticity

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