Cogan’s Syndrome with Cutaneous Findings: A Case Report and Review of Dermatologic Manifestations

Khasha Touloei, DO,* Emily Tongdee, BS,** Brittany Smirnov, DO,*** Tracy Favreau, DO,**** Leeor Porges, DO*

*Second-year Dermatology Resident, Nova Southeastern University College of Osteopathic Medicine / Broward General Medical Center, Ft. Lauderdale, FL
**Third-year Medical Student, Florida International University Herbert Wertheim College of Medicine, Miami, FL
***First-year Dermatology Resident, Nova Southeastern University College of Osteopathic Medicine / Broward General Medical Center, Ft. Lauderdale, FL
****Director/Chairman of Dermatology, Nova Southeastern University College of Osteopathic Medicine / Broward General Medical Center, Ft. Lauderdale, FL

Abstract

Cogan’s syndrome (CS) is a rare autoimmune disease characterized by ocular and vestibuloauditory symptoms, occasionally presenting with vasculitis. Although rare, dermatologic manifestations often compel patients to seek medical attention. Classically associated with vasculitis, cutaneous findings vary widely, making it vital for dermatologists, neurologists, rheumatologists, and primary care physicians alike to consider CS in any patient with ocular and vestibuloauditory symptoms, especially with dermatologic findings.

We report a rare case of CS with dermatologic findings, reviewing the literature for its classification, epidemiology, etiology, pathophysiology, and current therapeutic approaches. We emphasize the spectrum of cutaneous findings, which spans from non-specific skin rashes and urticarial vasculitis to palpable purpura and pyoderma gangrenosum.

Coexisting cutaneous conditions can delay diagnosis, affecting patient outcome particularly in reference to permanent sensorineural hearing loss. Irreversible loss of visual acuity can also result from delayed treatment. Dermatologic findings may direct physicians to CS and prevent severe negative outcomes.

Introduction

The first case of non-syphilitic keratitis in association with audiovestibular symptoms was reported in 1935 by Morgan and Baumgartner.1 In 1945, David Cogan reported four additional cases, and the syndrome was hence termed Cogan’s syndrome (CS).2 CS is a rare vasculitis whose hallmark features are non-syphilitic interstitial keratitis and audiovestibular symptoms similar to Meniere’s syndrome, including hearing loss, tinnitus, and vertigo.4 By 1980, Haynes et al. defined atypical CS, a variant wherein patients present with ocular and audiovestibular symptoms other than the interstitial keratitis and Meniere’s-type symptoms characteristic of the typical variant.5

The pathophysiology of CS is believed to be autoimmune in nature, initially supported by the positive response to corticosteroids.1 Western blots and immunofluorescence eventually revealed autoantibodies to the inner ear, including both anti-neutrophilic cytoplasmic antibodies (ANCA) and anti-endothelial antibodies.5,6,9 CS has been described most commonly in Caucasians, with no reported sex predisposition.6,7 Pediatric Cogan’s syndrome, however, affects males more than females by a ratio of 2:1.4 Both typical and atypical CS generally present between the second and fourth decades of life, although other sources suggest the first three decades.3,4 The age of onset of pediatric CS cannot be specified due to the low number of cases reported in the literature.4 Disease course varies, but it most often becomes chronic and slowly progressive following an initial flare.10 This article will focus on both variants of CS and review the literature of dermatologic findings in CS.

Case Report

A 47-year-old Trinidadian male presented with a two-month history of progressive loss of visual acuity and bilateral hearing, as well as headache and a rash that developed over six days on the dorsum of his hands bilaterally (Figure 1). The patient reported that similar symptoms initially began one year prior, during which time he presented to and was discharged from the emergency room without intervention. The patient reports that the rash began as a single papule on the left lateral hand, enlarged and then eventually ulcerated to become what he described as looking like a “cigarette burn.” Review of
systems was positive for pruritus and vertigo.

Physical examination revealed a Fitzpatrick 3 patient with erythematous, crusted papules and plaques on the dorsal lateral hands and digits and light brown, reticulated hyperpigmentation on bilateral lower extremities, with splinter hemorrhages on the right hallus and petechiae on the bilateral toes (Figures 1, 2). Ocular examination revealed bilateral inferior conjunctival erythema. Ophthalmologic consultation diagnosed the patient with anterior scleritis and scleromalacia.

Two biopsies were performed for hematoxylin and eosin (H&E) staining as well as a lesional direct immunofluorescence (DIF) to rule out Buerger’s disease or any other form of vasculitis. Biopsy revealed spongiotic dermatitis with overlying crust, and DIF was negative and thus non-diagnostic (Figure 3). An extensive workup was performed to rule out vasculitis, with all studies being negative. An autoimmune workup for lupus was negative. Additionally, the patient was negative for HIV and RPR. MRI scan of the brain revealed a right basal ganglia, left external capsule, and left central semiomental infarct. The constellation of ocular inflammation (diagnosed as scleritis), bilateral hearing loss, thrombocytosis, pruritic skin lesions, and elevated ESR and CRP was consistent with CS.

![Image](https://via.placeholder.com/150)

**Figure 3. H&E biopsy from the right dorsal hand.**

**Discussion**

CS is a clinical diagnosis based on ocular inflammation, audiovestibular symptoms, negative serologic syphilis tests, and histological evidence of vasculitis. However, due to the variability of symptoms and lack of specific tests, CS is best retrospectively diagnosed after responsiveness to corticosteroid treatment. Dermatologic symptoms can be the impetus for CS patients seeking treatment, so the condition should be considered when certain dermatologic findings present along with the constellation of symptoms characteristic of CS (keratitis, scleritis, vertigo, and hearing loss). Although our patient presented with a biopsy indicating hemorrhagic crusted scabs and ulcers, other dermatologic findings have also been documented. The few skin manifestations reported among CS patients have varied from non-specific erythematous or urticarial rash, purpura, nodules or ulceration of the limbs, genitals or mouth, pyoderma gangrenosum, and limbal erythema. In an analysis of 24 pediatric cases, only three presented with cutaneous manifestations of skin rash and urticarial vasculitis. Although musculoskeletal, ocular, and vestibular symptoms improved throughout the disease course, cardiovascular and skin manifestations did not. In this study, a delayed diagnosis was related to a worse outcome. Additionally, among 50 case reports of CS, only four presented with dermatologic findings. These findings included a transient macular rash, a hemorrhagic, ulcerated vasculitis rash, and two cases complicated by pyoderma gangrenosum. One case emphasized the significance of an early diagnosis to prevent hearing loss, while another highlighted how isolated systemic manifestations may delay diagnosis if ocular and audiovestibular symptoms are absent.

A common problem in the diagnosis of CS patients is the variability of disease progression over time. As evidenced by Zulian et al., hallmark symptoms do not follow a chronological timeline. In that study, a 4-year-old Caucasian boy developed conjunctivitis 10 days prior to admission. Although hallmarch symptoms may occur within years of one another, this patient developed sensorineural hearing loss soon after admission. However, in many cases it is not until much time has passed, often after many misdiagnoses, that the patient finally presents with the second of the two hallmarks. By that time, physicians may not associate the two symptoms, making it difficult to diagnose the symptoms as a syndromic event, let alone as a rare condition such as CS. Despite being an uncommon presentation, dermatologic manifestations can help clue physicians in to CS, especially when the patient does not have a history of both hallmark features.

The significance of early diagnosis cannot be stressed enough, especially in pediatric cases of CS. This is due to the positive outcomes associated with early treatment via immunosuppression. Systemic symptoms tend to fully resolve upon treatment. Most important, though, vision and hearing loss can be reversible or irreversible depending on the extent of delay from illness onset to time of treatment. Orsoni et al. present a case report of two children with CS, both treated with corticosteroid-sparing immunosuppression. While both children’s systemic symptoms resolved, one child’s visual acuity and hearing loss improved whereas the second child had no ocular or auditory improvement. Given the devastating effects of irreversible deafness and vision loss, awareness of less-common presentations, such as those of the skin, can decrease the occurrence of not just negative outcomes, but permanent negative outcomes.

**Pathophysiology**

CS is mediated by lymphocytic and plasma-cell infiltration of the corneal and cochlear tissue. Autoantibodies targeting corneal, inner ear, and endothelial antigens have been found to be specific to CS. More specifically, IgG antibodies against the inner ear were identified in CS patients, in addition to IgG, IgM, and IgA antibodies against the cornea. Other autoantibodies, such as ANCA and rheumatoid factor (RF), have also been reported but remain non-specific due to their prevalence in other rheumatologic and autoimmune conditions.

One study found an immunodominant autopeptide common among eight CS patients that showed similarities to antigens such as SSA/Ro and the reovirus III major core protein lambda 1. The autopeptide was also similar to cell-density enhanced protein tyrosine phosphate-1 (DEP-1/CD148), a protein expressed on sensory epithelia of the inner ear and on endothelial cells. In CS, IgG antibodies bind to cells expressing DEP-1/CD148 and inhibit cell proliferation. Antibodies targeting heat shock proteins 70 and 68kDa derived from bovine inner ear have also been reported. All the aforementioned cochlear-targeting autoantibodies were originally thought to be specific for CS but were later found in children with idiopathic sensorineural hearing loss.

**Etiology**

The exact etiology of CS remains unknown; however, various hypotheses have been proposed. It is possible that an infection may trigger CS, given that upper respiratory tract infections precede 21% of cases. Another theory is that CS may be associated with Chlamydia infections or tuberculosis vaccination. In support of the theory of infection, some HLA loci, including HLA-B17, HLA-A9, HLA-Bw35, and HLA-Cw4, correlate with CS.

**Presentation**

CS primarily presents with bilateral interstitial keratitis with audiovestibular symptoms. In addition to its hallmark features, CS may also present with systemic, cardiovascular, neurologic, and gastrointestinal manifestations. Skin manifestations are not commonly seen but do occur rarely. The presentation varies slightly between typical and atypical CS.

The clinical criteria for typical CS include nonsyphilitic interstitial keratitis, audiovestibular symptoms similar to Meniere’s syndrome, and an interval between the onset of the first two criteria of less than two years. Ocular symptoms are usually bilateral. Audiovestibular symptoms can develop at any time throughout the disease course and commonly include hearing loss, vertigo, tinnitus, ataxia, and oscillopsia. Systemic manifestations may be present secondary to vasculitis of all vessel sizes, with complaints of headache, arthralgia, fever, arthritis, and myalgia being most common. Aortitis with aortic insufficiency is a major cardiovascular manifestation that occurs in 10% of patients. Neurological symptoms include sensorineural hearing loss but also extend to hemiparesis or hemiplegia secondary to a cerebral vascular accident and aphasia secondary to a transient ischemic event. Finally, gastrointestinal
manifestations may range from diarrhea and melena to abdominal pains, presumed to be due to mesenteric arteritis.26

The clinical criteria for atypical CS include various inflammatory ocular symptoms (with or without interstitial keratitis), audiovestibular symptoms unlike Meniere’s syndrome, and more than two years between the onsets of the first two criteria.3

Ocular manifestations that separate atypical from typical CS include acute closure angle glaucoma, retinal vasculitis, papillitis, central vein occlusion, vasculitic optic neuropathy, and papilledema.22

The systemic vasculitis of atypical CS involves the cardiovascular, neurologic, and gastrointestinal systems, unlike in typical CS.24 Differentiation between typical and atypical CS may be difficult due to variability in the progression of the disease. However, systemic manifestations occur more often in atypical CS and can thus be used to distinguish between the two.3

**Differential Diagnosis**

CS needs to be diagnosed early to prevent the onset of severe hearing loss.23 The differential diagnosis of CS includes syphilis, Vogt-Koyanagi–Harada (VKH) syndrome, and Meniere’s syndrome.24 Diagnosis may be difficult during the onset of CS due to audiovestibular similarities to Meniere’s syndrome. The loss of balance and ataxia present in CS differ from the typical vertigo of Meniere’s syndrome, which can help differentiate the two.

Furthermore, Meniere’s does not present with ocular symptoms. VKH is a multisystem disease that includes uveitis, leukokerma, sensorineural deafness, alopecia, and poliosis. CS does not present with alopecia or poliosis. More important, VKH presents with a severe exudative uveitis not seen in CS.24 Finally, syphilis mimics CS with an acute onset of bilateral audiovestibular symptoms.24 However, the interstitial keratitis in syphilis is chronic, not acute, and does not show active inflammatory changes. Upon slit-lamp examination of the deep cornea, a vascular infiltrate can be seen as ghost vessels in patients with syphilis. A significant difference between CS and syphilis is that patients with syphilis present with infiltrate more central to the cornea.24
Other Cases

Although CS is not characteristically described to present with dermatologic manifestations, there have been several reports. Table 1 summarizes dermatologic symptoms described among various case reports of CS.

Treatment

Medical treatment varies based on symptom severity and the extent of the disease. Steroid treatment is the common therapy no matter the degree of severity. Mild eye symptoms warrant the use of topical glucocorticoids and cycloplegics.3 Topical cyclosporine A has also been found to be effective in severe anterior segment inflammation.34 However, when there is posterior segment inflammation, systemic treatment is the preferred treatment of choice. Due to the pathophysiologic of CS, which involves various organs (primarily the inner ear, the eye, and/or systemic vasculitis), immunosuppressive therapy is the goal. Systemic corticosteroids are the gold standard of care.3

As previously mentioned, early treatment is important in CS due to the progressive audi vesitubular degradation that may be irreversible if left untreated for too long. The moment audi vesitubular dysfunction is noted, high-dose corticosteroids should be administered (1 mg/kg to 1.5 mg/kg of prednisone daily).3 Signs of reversal of audi vesitubular symptoms should be noticed within two to three weeks.24,34 Following improvement, the steroid dose should be slowly decreased and continued for two to six months.3 Infliximab in particular seems effective if started during the beginning of inner-ear damage. It has also been useful in maintenance of remission in CS patients with treatment failure.12,13 If sensorineural hearing loss progresses due to treatment failure, cochlear implant surgery is suggested.1

If corticosteroid therapy is contraindicated or the treatment regimen fails, other immunosuppressants, such as cyclophosphamide, azathioprine, methotrexate, cyclosporine and tumor necrosis factor-alpha blockers, should be used.35,40–42

Conclusion

Skin manifestations among CS patients are rare; nevertheless, it is important to report unusual cases such as this one, especially with less common findings, as they add to the pre-existing pool of literature and further the understanding and identification of varying presentations of such a rare condition.

Cutaneous manifestations of CS present along a spectrum, from non-specific skin rashes and urticarial vasculitis to palpable purpura and pyoderma gangrenosum. These coexisting conditions can delay diagnosis, which can profoundly affect the patient outcome, particularly in reference to permanent sensorineural hearing loss. Irreversible loss of visual acuity can also result from delayed diagnosis and subsequent delayed treatment. Although they are the least likely of systemic manifestations, dermatologic findings are often the impetus for patients to seek healthcare, highlighting the importance of recognizing these presentations of CS.

References


Correspondence: Emily Tongdee, BS; etong001@fiu.edu