COGAN'S SYNDROME WITH TAKAYASU'S ARTERITIS

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SUMMARY
Cogan’s syndrome may be associated with large-vessel arteritis. We describe a patient with ocular inflammation, sensorineural hearing loss and arm claudication in whom a diagnosis of ‘atypical’ Cogan’s syndrome and Takayasu’s arteritis was made. All symptoms resolved with treatment.

KEY WORDS: Cogan’s syndrome, Takayasu’s arteritis, Steroids, Methotrexate.

In 1945, Cogan described a syndrome of interstitial keratitis and vestibuloauditory symptoms [1]. While interstitial keratitis is necessary for the diagnosis of ‘typical’ Cogan’s syndrome [2], other types of inflammatory eye disease, including conjunctivitis, uveitis, scleritis and choroiditis, have been widely recognized, and their association with the vestibuloauditory abnormalities has been termed ‘atypical’ Cogan’s syndrome [2, 3]. Auditory involvement manifests as sensorineural hearing loss, vertigo and tinnitus. Patients with Cogan’s syndrome may exhibit systemic features. In a case series and review of the literature, half the patients had fever and weight loss, 14% had aortic insufficiency and 15% had vasculitis, involving large, medium or small vessels [4]. As with all such surveys, there is likely to be a bias towards unusual and severe cases, and the actual frequency of systemic manifestations in Cogan’s syndrome may be much lower.

Takayasu’s arteritis is a chronic inflammatory disease, affecting predominantly large arteries, with narrowing, occlusion or dilatation in the involved segments. A ‘trihasic’ pattern of disease progression has been described [5]. Phase 1 is the early inflammatory period, characterized by non-specific complaints including fever, arthralgia and weight loss. Phase 2 involves vessel inflammation, with associated pain and tenderness. Phase 3 is the late fibrotic stage, in which stenoses of the aorta and its major branches or the pulmonary arteries predominate. In practice, such progression from one phase to the next is not always seen. Ocular and auditory involvement in Takayasu’s arteritis is rare. Where such involvement is seen, there is considerable overlap with Cogan’s syndrome.

We report the clinical course of a 58-yr-old woman who fulfills criteria for classification as both Takayasu’s arteritis and ‘atypical’ Cogan’s syndrome. Despite initial disease control with oral steroids, her condition relapsed with deterioration of hearing. Treatment with i.v. steroids, prostaetacyclin and aspirin resulted in marked improvement. A second relapse was controlled with pulsed i.v. cyclophosphamide administered over a 4 month period, and remission was maintained with methotrexate and very-low-dose prednisolone.

CASE REPORT
A 58-yr-old Caucasian woman presented with a 4 month history of lethargy, nausea, weight loss, sweats, and pain in her left arm exacerbated by use. She had had ear pain and hearing loss, worse on the left, for 1 month. A few days before presentation, she developed painful red eyes with photophobia. There was no headache, scalp tenderness, jaw claudication, hair loss or angina. She had previously been well, and was taking no medications. She did not smoke and drank only occasional alcohol. There was no significant family history.

Physical examination revealed a pulse of 88 with decreased left brachial artery pulse. Blood pressure was 125/70 mmHg in the right arm and 95/70 mmHg in the left. Heart sounds were normal and there was a left subclavian bruit. There was no arterial tenderness and the lower limb pulses were normal. Acuity was 6/18 in the right eye and 6/12 in the left. There was diffuse episcleritis bilaterally with mild anterior uveitis on slit-lamp examination. The outer ears were normal and there was bilateral sensorineural hearing loss, worse on the left. There was no synovitis, lymphadenopathy, tenderness or decreased pulsation of the temporal arteries.

Laboratory tests revealed an erythrocyte sedimentation rate (ESR) of 106 mm/h and a C-reactive protein (CRP) of 71 mg/l (<6). She was borderline positive for rheumatoid factor at 42 IU/ml (<30), other autoantibodies being negative. Immunoglobulin and complement levels were normal, and factor VIII-related antigen elevated at >3.1 IU/ml (1.1–2.4). Electrolytes and creatinine were normal, creatinine clearance was 80 ml/min, 24 h urinary total protein excretion 0.05 g (<0.2), and there were no white cells, red cells or casts in the urine. Her differential blood count, calcium, albumin, alkaline phosphatase, transaminases and thyroid function tests were normal. Syphilis, hepatitis and Chlamydia serology were negative. Chest radiograph and ECG were normal, and an echocardiogram showed mild aortic regurgitation. An aortic arch angiogram and selective angiogram of the left subclavian artery showed narrowing of the left subclavian artery over a 4 cm segment distal to the internal mammary artery (felt to be consistent with Takayasu’s arteritis) (Fig. 1). Audiograms confirmed high-frequency hearing loss.

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sensorineural hearing loss, worse in the left ear. Air conduction audiograms are shown (Fig. 2). In the absence of local symptoms and signs, temporal artery biopsy was not performed as it was felt that it would not influence management.

‘Atypical’ Cogan’s syndrome with Takayasu’s arteritis was diagnosed on the basis of bilateral inflammatory eye disease, sensorineural deafness and the presence of five of the six American College of Rheumatology 1990 criteria for the classification of Takayasu’s arteritis (arm claudication; decreased brachial artery pulse; >10 mmHg difference in systolic blood pressure between the two arms; subclavian bruit; angiographic narrowing of a large upper extremity artery) [6]. Sixty milligrams of daily oral prednisolone, and dexamethasone and atropine eye drops were started. Her general condition and hearing improved, the ocular inflammation, asymmetry in arm blood pressure, subclavian bruit and acute-phase response settled, and the dose of steroids was gradually reduced to 15 mg/day. At week 6 her hearing deteriorated, particularly in the left ear. Prednisolone was increased to 40 mg/day with little improvement over 1 week. Audiograms at week 7 confirmed the deterioration in hearing (Fig. 2). She was given a pulse of 1 g i.v. methylprednisolone, a 3 day prostacyclin infusion, and low-dose aspirin. Hearing improved in both ears (Fig. 2). Azathioprine was added to oral prednisolone for its steroid-sparing effect, but had to be discontinued due to a rash. Once oral steroids were reduced to 20 mg/day, her condition deteriorated, with malaise and further left arm pain. Prednisolone was re-increased to 40 mg/day, with no improvement, and 2 weeks later she was given i.v. cyclophosphamide (15 mg/kg) and methylprednisolone (10 mg/kg), which was repeated five times over the next 15 weeks, with resolution of her symptoms. She went into complete clinical and serological remission, which was maintained with low-dose oral methotrexate (7.5 mg/week).

Repeat echocardiogram showed no evidence of aortic regurgitation and radiographs showed no erosive changes in the hands or wrists. Her prednisolone was gradually reduced over the next 15 months until she was taking only methotrexate and 1 mg/day prednisolone with no recurrence of her symptoms.

**DISCUSSION**

The incidence of Cogan’s syndrome is not known. It is a disease of young adults, with a median age of onset of 25 yr [4]. There is no gender preponderance [4]. The aetiology is unknown. Immune mechanisms have been implicated. A minority of patients with Cogan’s syndrome demonstrate rheumatoid factor, antinuclear antibodies and diminished complement levels [7]. Histology of involved tissue often reveals vasculitis and perivascular inflammation [7]. An infectious aetiology has also been postulated. *Chlamydia psittaci* has been isolated from a patient with Cogan’s syndrome [8], and serological evidence of recent *Chlamydia trachomatis* infection was reported in four of 13 patients [3]. There was no evidence of chlamydial infection in our patient.

A plethora of reports from the Far East has led to a stereotyped impression of patients with Takayasu’s arteritis as young Oriental women. In Japan, it has been estimated that there are ~100 new cases per year [9]. However, the disease is becoming increasingly recognized worldwide. A North American study reported an incidence of 2.6 cases per million per year [10], suggesting an incidence similar to that in Japan. Eighty to 90% of patients are females [9], unlike the situation in Cogan’s syndrome. In most cases, the disease begins between the ages of 10 and 30 yr [11]. In a large Japanese survey, Takayasu’s arteritis began between the ages of 50 and 59 yr in only 3.4% of cases, as in the patient described [9]. Atherosclerotic disease and giant cell arteritis (GCA) must be considered in older patients with narrowing of the aorta or its primary branches. The resolution of arm claudication,
increase in brachial artery blood pressure, disappearance of the subclavian bruit and the aortic regurgitation all mitigate against a fixed atherosclerotic lesion in this case. The absence of headache or temporal artery abnormality on examination made the diagnosis of GCA less likely. Nevertheless, the patient fulfilled two of the American College of Rheumatology 1990 criteria for the classification of GCA [12]. Had temporal arteritis been demonstrated histologically, three of the five criteria would have been fulfilled, sufficient for classification as GCA. This illustrates the overlap in classification criteria that may be seen in vasculitis.

There are no randomized clinical trials to guide therapeutic decisions in these conditions. In Cogan’s syndrome, ophthalmic manifestations may be treated successfully with topical steroids [2]. However, systemic therapy is necessary for audiovestibular and systemic features [2]. Steroids are regarded as the mainstay of therapy. There have been reports of the use of methotrexate [13], azathioprine [4], cyclophosphamide [4] and cyclosporin [14] to control disease activity. The ophthalmic outcome in Cogan’s syndrome is usually very good [2]. Hearing loss, however, is often irreversible, although the early use of steroids may result in improvement [4]. In a literature review, 12 of 36 patients with Cogan’s syndrome had improvement of their hearing 1 week after beginning glucocorticoid therapy. Those patients who were already deaf when treatment was initiated were significantly less likely to have improved hearing [4].

There has been more experience in managing Takayasu’s arteritis, where treatment with steroids may suppress systemic symptoms and reverse arterial stenoses in the early stages of disease [15]. Initial doses of 40–60 mg/day of prednisolone are often given, and the dose reduced as symptoms and laboratory markers of inflammation settle. In a study of 12 patients treated with steroids, fatigue disappeared in all, and arm claudication resolved in five of eight patients [16]. In another study, six of 16 patients had angiographic progression of their vascular lesions after 3 months of prednisolone [15]. Cytotoxic drugs are added if steroids are ineffective, or to reduce the required dose of steroid, but the choice of agent is controversial. Both cyclophosphamide [15] and methotrexate [17] have been used successfully. It has been argued that methotrexate should be used in preference because of a lower risk of side-effects [5]. Although prolonged remission is seen the disease often follows an indolent course with intermittent exacerbations [5] requiring long-term immunosuppressive therapy.

In this case, reduction in the dose of oral steroids was followed by relapse, with significant hearing impairment. Remission, with marked improvement in hearing, was achieved with i.v. steroids, prostacyclin and aspirin. Our rationale for using vasodilator and antiplatelet drugs was that inflammatory endothelial cell injury in vasculitis may lead to decreased local production of vasodilators, and platelet adhesion to damaged blood vessel walls [18]. An attempt to maintain remission with azathioprine was unsuccessful because of drug intolerance. The second relapse was managed successfully with pulsed i.v. steroids and cyclophosphamide followed by oral methotrexate. The duration of cyclophosphamide treatment in systemic vasculitis is controversial, but there is some evidence that the majority of the response occurs in the first 3 or 4 months, and it may be that if remission is achieved in this time, then less toxic agents can be used for maintenance [19]. The patient is currently maintained in remission with methotrexate and very-low-dose prednisolone.

This case illustrates the overlap between Takayasu’s arteritis and the inflammatory ocular and auditory features of Cogan’s syndrome. It suggests that hearing loss in Cogan’s syndrome may be reversed with the early use of immunosuppressive therapy in conjunction with prostacyclin and aspirin, while remission may be maintained using methotrexate and very-low-dose prednisolone.

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REFERENCES