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Diagnostic Difficulties of Cogan Syndrome

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Abstract

Cogan's syndrome (CS) is a very rare disorder of unknown origin characterised by inflammatory eye disease and vestibuloauditory symptoms. According to the International Chapel Hill Consensus Conference Nomenclature of Vasculitides, CS is defined as "variable vessel vasculitis". We present the case of a 44-year old male, primarily diagnosed and treated for large/medium vessel vasculitis probably due to indeterminate colitis, who finally developed CS. Difficulties in the diagnosis of this rare disease are also discussed.

Keywords: Cogan syndrome; Exophtalmos; Inflammatory eye disease; Chronic diarrhea; Sudden hearing loss

Introduction

Cogan's syndrome (CS) is a rare disorder characterised by inflammatory eye disease and vestibuloauditory symptoms. In about 30% of cases it can be associated with other systemic inflammatory manifestations such as fever, arthralgia, skin rash, gastrointestinal tract involvement and vasculitis [1]. Vasculitic manifestations include mainly arteritis affecting small, medium or large arteries and according to the International Chapel Hill Consensus Conference Nomenclature of Vasculitides, CS is defined as "variable vessel vasculitis" [1]. The onset of the disease is preceded in approximately 20% of cases by an infection, especially Chlamydia psittaci [2] and Chlamydia trachomatis [3]. Recent evidence strongly suggests that CS is an autoimmune disease that is mediated by a hypersensitive response to infectious agents associated with vasculitis [3-5]. We present the case of a 44-year old male, primarily diagnosed and treated for large/medium vessel vasculitis probably resulting from indeterminate colitis, who developed CS with inflammatory eye disease and vestibuloauditory symptoms. We discuss the diagnostic difficulties in this rare disease.

Case Report

A 44-year old male, a pigeon-fancier, was admitted to the hospital due to general weakness secondary to recurrent periods of fever (maximum 38.5°C), chronic watery diarrhea accompanied by severe headache and ophthalmopathy with decreased vision. All the symptoms occurred several months before hospitalization and gradually intensified. Physical examination revealed only bilateral exophthalmos. Laboratory tests had shown leukocytosis (white blood cell count 17.9 10^9/l), thrombocytosis (platelet count 600 10^9/l), mild anemia (hemoglobin level 11,6 g/dl), marked elevation of inflammatory markers (ESR 100 mm/h, CRP 10.9 mg/l) and an active urine sediment. Based on laboratory, serological and microbiological test, immunodeficiencies, Lyme disease, toxoplasmosis, the most common viral infections (hepatitis B and C, cytomegovirus and HIV), atypical respiratory (Mycoplasma pneumonia and Chlamydia pneumonia) and urogenital (Ureaplasma urealyticum) infections were excluded. The blood, urine and stool cultures were also negative. Ophthalmological examination revealed changes suggestive of viral or autoimmune aetiology (Figure 1). Despite empiric antibiotic therapy (amoxicillin with clavulanic acid, ciprofloxacin) there was no clinical improvement and elevated leukocytosis, and inflammatory markers were still present (Table 1). Diagnostic Computed Tomography (CT) of the head, neck, thorax and abdomen, magnetic resonance imaging (MRI) of the orbits, echocardiography, carotid and thyroid Doppler ultrasound imaging were performed. Pathological findings included inflammatory infiltration of the adipose tissue of the right orbit, a narrowing of both the left subclavian artery and the left internal carotid artery with thickening of the wall up to 3 mm. Gastroscopy revealed chronic gastritis (confirmed by histopathology). Despite the absence of inflammatory lesions in the intestine in colonoscopy, the histopathological examination revealed non-specific chronic colitis. The patient was negative for antinuclear antibody (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA). Immunological tests revealed only the presence of anti-Saccharomyces cerevisiae antibodies (ASCA) and immunological complexes (Table 1). Thyroid dysfunction was excluded as a reason for the ophthalmopathy (normal levels of thyroid hormones, no anti-TSH antibodies). Multiple organ involvement, laboratory (leukocytosis, thrombocytosis, mild

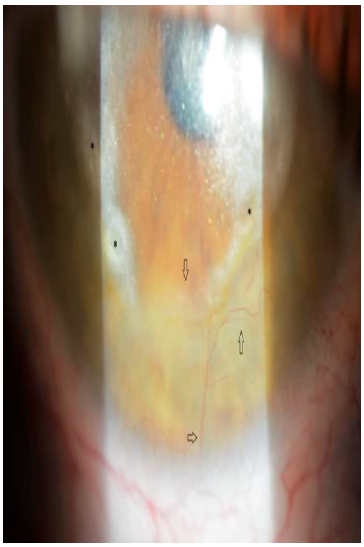

Figure 1: Right corneal lesions in the slit-lamp examination. Circular scars in the cornea (asterix), corneal infiltrates (best seen on the background of the pupil and around it), superficially and deeply ingrown vessels (arrow).

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anemia, marked elevation of inflammatory markers), imaging (thickening of the arterial walls) and immunological (lack of ANCA, the presence of antiendothelial cell antibodies), after exclusion of active infections, led to the most probable diagnosis of the large/medium vessel vasculitis in the course of indeterminate colitis. A total dose of 2.5 g (5 × 500 mg) of intravenous (iv.) methylprednisolone with subsequent oral steroid therapy (prednisone 1 mg per kg per day) in tapered doses and azathioprine (2 mg per kg per day) were administered. Central ulceration of the left cornea was initially treated with antibiotics in drops (levofloxacin and azithromycin) and then a solution of 0.1% dexamethasone and 0.05% cyclosporine in eye drops was used to reduce extant symptoms in both eyes. Regression of the exophthalmos, relief of the diarrhea and fever, as well as general improvement were achieved. The inflammatory bowel disease (IBD) was finally excluded by gastroenterologists on the basis of magnetic resonance enterography and double-performed histopathological examination of the intestinal wall.

During the following twenty months there were periods of exacerbations and improvement in ophthalmic changes (exophthalmia, conjunctival chemosis) as well as in inflammatory markers in laboratory tests (but these were not so high as before the immunosuppressive treatment). The patient was treated with prednisone (the average dose

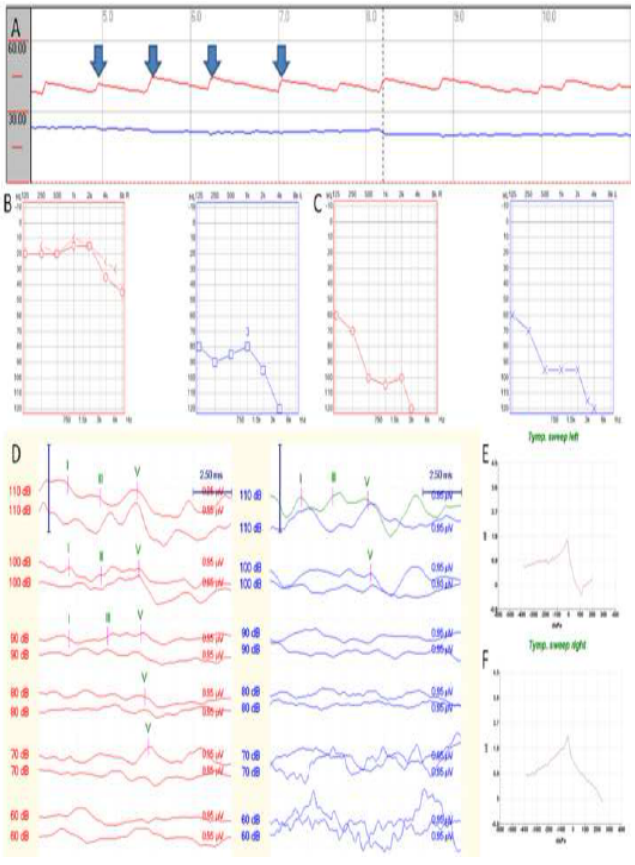

Figure 2: Audiovestibular tests. Videonystagmography (VNG) revealed spontaneous right-beating horizontal paralytic nystagmus (arrows show rapid phase of nystagmus) (**a**). Initial pure tone audiometry (PTA) (**b**) – severe to profound left-sided sensorineural hearing loss of – 86.7 dBHL (0.5-1-2 kHz) (blue), mild high-frequency sensorineural hearing loss (red). Final PTA (**c**) – bilateral profound sensorineural hearing loss. Brainstem Auditory Evoked Potentials (BAEPs) performed during treatment showed normal morphology, waves I, III, V latencies – cross check of type and degree in high-frequency hearing loss (click 2-4 kHz) (**d**). Tympanometry type A after Jerger classification indicated normal middle ear function (**e,f**).

20 mg, daily) and ciclosporine (150 mg twice a day) orally, and both 0.1% dexamethasone and 0.05% ciclosporine topically in eye drops. Two twenty two months after the onset of the initial symptoms, even though continuous immunosuppression has been provided, the patient suffered sudden left sensorineural hearing loss with vertigo, paralytic right-beating horizontal-rotatory nystagmus (Figure 2a) and tinnitus with accompanying nausea and fever. In Romberg's test he fell to the left, indicating the free phase of nystagmus. Otolaryngological examination revealed no abnormalities. Pure tone audiometry (PTA) showed left-sided sensorineural hearing loss (Figure 2b). Videonystagmography (VNG) revealed left canal paralysis. In addition to immunosuppressive therapy, lidocaine, hydrocortisone, pentoxifylline and vitamins (B1 and B6) were applied but with no hearing improvement. Despite treatment, after two weeks the patient developed right-sided sensorineural hearing loss and the left-sided hearing loss was intensified. There was no hearing improvement after systemic steroids either (Figure 2c). Brainstem auditory evoked potentials (BAEPs) (Figure 2d) revealed no retrocochlear type of hearing deterioration. The result of a tympanometric examination was normal (Figure 2e and 2f). The patient reported persistent tinnitus localised in both ears, which was slightly reduced after the use of a hearing-aid in the right ear. In the meantime fluid in the right sub-Tenon's space and the rotary horizontal nystagmus to the right were observed. In laboratory tests inflammatory markers (ESR 79 mm/h, CRP 266 mg/l) and leukocytosis (WBC 27.1 10^9/l) were elevated, but ANCA remained negative (Table 1). During the following week the same symptoms appeared in association with the other ear. A series of treatments in a hyperbaric chamber was prescribed as additional therapy but with no improvement. Blurred vision with aggreveated corneal lesions, in this circumstance recognized as interstitial keratitis (IK), also reappeared. Based on clinical presentation, the symptoms of inflammatory eye disease with vestibuloauditory involvement as well as large/medium vasculitis recognized 2 years earlier led us to identify vasculitis in CS. Methylprednisolone infusion and cyclophosphamide (CYC) treatment was then administrated. A total dose of 7.0 g of CYC was given in 1.0 g i.v pulses every three weeks. In view of the patient's long-term contact with pigeons,

suspecting infectious background of the exacerbations, the antibodies against Chlamydophila psittaci were checked, and IgA antibodies were present. Taking into account described in the literature the relationship between Chlamydophila psittaci infection and CS it was decided to antibiotics. Macrolide antibiotic treatment was administrated for three months (Azithromycinum 500 mg, daily three days in a week) in conjunction with immunosuppressive therapy.

After six months of treatment partial remission was achieved. Ultrasound of the eye showed more severe bilateral thickening of the back wall of the eyeball in the right eye. Moreover, the wall of the right eyeball was irregular and a "T-sign" was present (Figure 3). Spectral Domain Optical Coherence Tomography showed the actual position of corneal scars and confirmed ectasia of the cornea (Figure 4). For the time being, the patient remains under the rheumatologic and ophthalmologic care. Immunosuppressive treatment is still ongoing at the time of the writing (prednisone 30 mg, daily and azathioprine 100 mg, daily orally, as well as 0.05% ciclosporine twice a day and 0.1% dexamethasone once a day in eye drops).

Discussion

In 1980 Haynes et al. proposed diagnostic criteria for typical and atypical Cogan's syndrome (CS) according to the type of its ocular manifestations (Table 2) [3,6]. Presence of IK implies classification as typical CS. In atypical CS many other ocular lesions have been reported,

either in isolation or in association with IK. These include episcleritis or scleritis, retinitis, optical neuritis, glaucoma, papillary oedema, cataracts, ocular motor palsy, exophthalmia, central retinal artery occlusion, xerophthalmia, ptosis and tendonitis [3,6]. Exophthalmos was one of the initial symptoms in the presented case. Thyroid eye disease, the main cause of exophthalmos [7], was excluded in our patient. Improvement after immunosuppressive therapy was evidence of the autoimmune background of the disease [8-12]. Episcleritis is often linked to autoimmune diseases and it may also occur in CS [3,6]. In this case it was accompanied by unilateral posterior scleritis [3,9,13] appeared during ultrasonography of the eyeballs as the presence of fluid under the right sub-Tenon's space and thickening of the back wall of the eyeballs. We conclude that those changes were the dominant cause of

Laboratory test	Normal range	Results in the time of diagnosis of vasculitis	Results at the onset of vestibulocochlear symptoms
WBC (10^9/l)	4.0-10.0	17.9	27.1
Hgb (g/dl)	12.0-15.0	11.6	13.2
PLT (10^9/l)	150-410	600	203
ESR (mm/h)	2-30	100	79
CRP (mg/l)	0.0-5.0	10.9	266.4
Procalcitonin	<0.1 ng/ml	<0.1	<0.1
AlAT (U/l)	<55	23	26
AspAT (U/l)	5-34	14	12
GGTP (U/l)	9-36	262	35
Urine specific gravity	1.018-1.030	1.025	1.025
urine pH	5.0-8.0	5.5	5.0
RBCs in urine (HPF)	<3	4-10	4-10
WBCs in urine (HPF)	1-5	6-10	1-5
protein in urine	negative	trace	trace
TSH (IU/ml)	0.27-4.20	1.09	0.76
Ferrum (µg/dl)	59-158	24	25
Ferritin (ng/ml)	30-400	947	384
C3 (g/l)	0.9-1.8	2.0	np
C4 (g/l)	0.1-0.4	0.4	np
IgG (g/l)	7.0-16.0	18.03	np
IgM (g/l)	0.4-2.3	1.1	np
IgA (g/l)	0.7-4.0	3.02	np
ANA HEp2	1:100	1:100	np
anti-CCP (RU/ml)	0.0-5.0	2.7	np
ANCA (anti-neutrophil cytoplasmic antibodies)	<1:40	negative	negative
ANCA-PR3 (RU/ml)	<20	2.0	np
ANCA-MPO (RU/ml)	<20	2.0	np
ANCA-profile (anti-PR3, anti-LFE, anti-MPO, anti-CAT, anti-BPI)	<1.0	<0.1	np
Immunological complexes C1q (RU/ml) C3d (µg/ml)	<20 <40	68.2 77.3	11.9 0.03
Anti-TSH (TRAb) (IU/l)	<1.0	0.51	<20
ASCA (Anti-saccharomyces cerevisiae antibodies) (U/ml)	IgA <10 IgG <10	34.15 108.85	0.74 19.4
AECA (antiendothelial cell antibodies)	<1:10	1:10	1:20

np – not performed

Table 1: Laboratory test results.

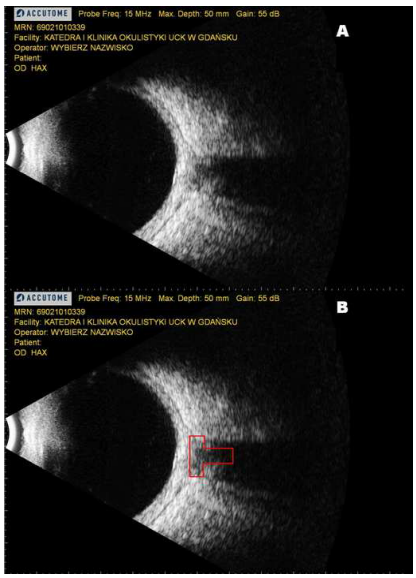

Figure 3: Ultrasound image of the right eyeball - HAX projection. (A) Thickening and irregular shape of the eyeball's back wall - "T-sign". (B) "T-sign" marked with red line.

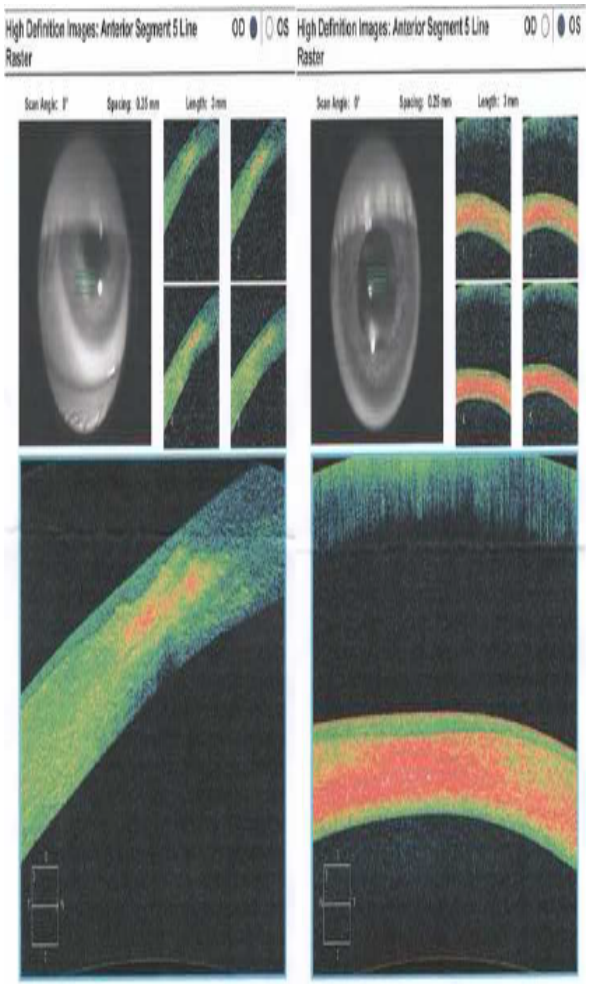

Figure 4: Spectral domain optical coherence tomography images of corneas. Scars located in the corneal stroma (reddish area). Concomitant tissue contraction (ectasia). Right eye (OD) on the left and left eye (OS) on the right side.

Typical Cogan's syndrome	
1.	ocular symptoms, non-syphilitic interstitial keratitis (IK)
2.	audiovestibular symptoms similar to those of Meniere's syndrome (sudden onset of tinnitus and vertigo, accompanied by graduał hearing loss)
3.	an interval between the onset of ocular and audiovestibular manifestations of less than 2 years
Atypical Cogan's syndrome	
1.	inflammatory ocular manifestations, with or without IK
2.	typical ocular manifestations associated with audiovestibular symptoms different from Meniere-like episodes
3.	a delay of more than 2 years between the onset of typical ocular and audiovestibular manifestations

Table 2: Diagnostic criteria for typical and atypical Cogan's syndrome.

the recurrent exophthalmos, repetitive disturbances in visual acuity in this case [9,12].

The audiovestibular manifestations associated with CS include sensorineural hearing loss, tinnitus, and vertigo. Recurrent episodes of inner ear disease frequently result in profound hearing loss, and the subject of the present case became completely deaf in about six weeks. In a retrospective series of 60 patients from one centre hearing loss was typically sudden, bilateral, fluctuating, and progressive, resulting in complete hearing loss in most cases [14]. Typically, audiometry testing demonstrates a sensorineural hearing loss, preferentially involving the low and high range frequencies. Hearing loss is often bilateral from the onset, but in some patients it may be unilateral initially, becoming bilateral later. In a review by Vollertsen et al. bilateral deafness affected 43.5% of patients and occurred on average three months after the onset of the initial symptoms [4].

The diagnosis of typical CS is made on the basis of non-syphilitic IK, acute-onset sensorineural hearing loss and vestibular symptoms such as Ménière's disease, and progressive hearing loss up to deafness within two years. Diagnosis of atypical CS can also be made when the classic pattern of autoimmune-type vestibuloauditory symptoms are associated with inflammatory eye disease other than IK or when the interval between the onset of the ophthalmological and that of the vestibuloauditory symptoms is more than two years. It is not easy to recognise whether CS is of the typical or atypical type, as several patients do not present IK at the onset and only develop this condition during the subsequent phase. The timing and association of manifestations of CS are extremely variable. As reported in the literature, there is frequently a prodrome very similar to a viral infection a few weeks preceding the onset of the disease. Both ophthalmological and vestibuloauditory symptoms appear within days or weeks of the disease onset. The case presented here followed a different course, greatly hindering proper diagnosis. Initially, because of the persistent diarrhea, the clinical picture suggested vasculitis secondary to Inflammatory Bowel Disease (IBD). It was only over a year that new symptoms, especially those involving the inner ear, enabled CS to be identified. We believe, that the eyes changes were the initial symptom of CS in this case.

The differential diagnosis of CS is made on the basis of various conditions that cause similar ocular and audiovestibular manifestations, polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), relapsing polychondritis, rheumatoid arthritis (RA), Susac's syndrome, Vogt-Koyanagi-Harada syndrome, sarcoidosis and giant-cell arteritis (GCA). In view of the absence of joint problems and lack of aCCP anibodies, RA was excluded in our patient. An absence of orogenital and mouth ulcerations, skin changes, patergy reaction, alopecia and vitiligo enabled us also to exclude Behçet's and Vogt-Koyanagi-Harada syndromes. Similarly, lack of changes in MRI of the brain allowed us to rule out Susac's syndrome. ANCA negativity and no symptomes of small vessel involvement led us to exclude ANCA-associated vasculitis. Similarly the fact that there was no typical presentation of upper and lower respiratory tract involvement led us also to exclude GPA. Ocular manifestations of giant cell arteritis have a different form than in CS.

There was still a suspicion of IBD as a cause of symptoms in our patient. It has been reported that there is an association between CS and IBD [15], and the high level of ASCA along with gastrointestinal symptoms made the diagnosis of IBD likely. Many studies have reported the simultaneous presence of ASCA IgA and IgG to be highly specific for Crohn's disease (CD). However, the absence of any typical changes in the microscopic bowel examination and in MRI ruled this disease out. In our opinion the gastrointestinal symptoms presented in our patient were the first sign of disease. Graslund et al. in their group of 32 patients with CS diagnosed 10 patients with gastrointestinal problems including abdominal pain, splenomegaly, hepatitis, oesophagitis and liver steatosis [6]. Various gastrointestinal manifestations, including diarrhea, melena and abdominal pain, sometimes related to mesenteric arteritis, have also been reported in the literature [4].

One of the factors potentially responsible for the development of the disease is chlamydial infection. There is some data in the literature concerning a link between CS and chronic chlamydial infection [2]. Long-term contact with pigeons, along with positive serology against Chlamydia psittaci, suggests chronic infection as a trigger for a CS in this case. Therefore, despite the presence of only IgA antibodies, it was decided to antibiotic therapy. Because of the absence of appropriate guidelines, the duration of treatment was based analogously to the treatment of chlamydial reactive arthritis.

The treatment of CS depends on the extent of the disease. If a mild eye involvement is the only manifestation, topical glucocorticoids are the treatment of choice. In cases of systemic vasculitis or hearing loss, however, systemic immunosuppressive therapy is required. Glucocorticoids (prednisolone 1 mg/kg) are the first-choice agents. If the response is incomplete, the addition of another immunosuppressive agent (methotrexate, cyclophosphamide, azathioprine, cyclosporine) should be considered [8]. Observations have also been made on the positive effect of rituximab [16], and anti-TNF blockers [17] in the treatment of patients with CS.

The prognosis for the maintenance of vision and the resolution of inflammatory eye lesions is generally good, but deafness generally remains permanent despite immunosuppressive treatment. An allogeneic corneal transplantation was considered to improve visual acuity [11]. Corneal transplantation may perhaps be possible in the future after stabilisation of the ocular lesions and the patient's general condition. Similarly, with respect to the deafness, cochlear implants are planned, as these are believed to be effective in patients with deafness in the course of CS.

One should also be aware of the potentially life-threatening complication of CS – vasculitis. Aortitis, which may develop within weeks to years of disease onset, has been described in approximately 10 percent of patients [3,8]. It may cause proximal aorta dilation, aortic valvular regurgitation, ostial coronary artery disease, and thoracoabdominal aortic aneurysms.

Conclusions

Cogan's syndrome is a rare autoimmune vasculitis with ocular and audiovestibular involvement. Atypical initial ophthalmologic symptoms

with predominant symptoms of gastrointestinal tract involvement may imitate IBD. The occurrence of audiovestibular symptoms associated with ophtalmologial changes indicates a correct diagnosis. Early assessment and treatment of the systemic inflammation are needed to prevent a complete loss of sight and hearing, and life-threatening complications, in particular, vasculitis such as aortitis.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, et al. (2013) 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65: 1-11.
2. Darougar S, John AC, Viswalingam M (1987) Isolation of Chlamydia psittaci from a patient with interstitial keratitis and uveitis associated with otological and cardiovascular lesions. Br J Ophthalmol 62: 709-714.
3. Haynes BF, Kaiser-Kupfer MI, Mason P, Fauci AS (1980) Cogan syndrome: studies in thirteen patients, long term follow-up, and a review of the literature. Medicine 59: 426-441.
4. Vollertsen RS (1990) Vasculitis and Cogan's syndrome. Rheum Dis Clin North Am 16: 433-439.
5. Schuknecht HF (1991) Ear pathology in autoimmune disease. Adv Otorhinolaryngol 46: 50-70.
6. Grasland A, Pouchot J, Hachulla E, Blétry O, Papo T, et al. (2004) Typical and atypical Cogan's syndrome: 32 cases and review of the literature. Rheumatology (Oxford) 43: 1007-1015.
7. Scott IU, Siatkowski MR (1999) Thyroid eye disease. Semin Ophthalmol 14: 52-61.
8. Vollertsen RS, McDonald TJ, Younge BR, Banks PM, Stanson AW, et al. (1986) Cogan's syndrome: 18 cases and a review of the literature. Mayo Clin Proc 61: 344-361.
9. Shah P, Luqmani RA, Murray PI, Honan WP, Corridan PG, et al. (1994) Posterior scleritis--an unusual manifestation of Cogan's syndrome. Br J Rheumatol 33: 774-775.
10. Allen NB, Cox CC, Cobo M, Kisslo J, Jacobs MR, et al. (1990) Use of immunosuppressive agents in the treatment of severe ocular and vascular manifestations of Cogan's syndrome. Am J Med 88: 296-301.
11. Miserocchi E, Baltatzis S, Foster CS (2001) A case of atypical Cogan's syndrome with uncommon corneal findings. Cornea 20: 540-542.
12. Sainz de la Maza M, Foster CS, Jabbur NS (1995) Scleritis associated with systemic vasculitic diseases. Ophthalmology 102: 687-692.
13. Cundiff J, Kansal S, Kumar A, Goldstein DA, Tessler HH (2006) Cogan's syndrome: a cause of progressive hearing deafness. Am J Otolaryngol 27: 68-70.
14. Gluth MB, Baratz KH, Matteson EL, Driscoll CL (2006) Cogan syndrome: a retrospective review of 60 patients throughout a half century. Mayo Clin Proc 81: 483-488.
15. Scharl M, Frei P, Fried M, Rogler G, Vavricka SR (2011) Association between Cogan's syndrome and inflammatory bowel disease: a case series. J Crohns Colitis 5: 64-68.
16. Orsoni JG, Laganà B, Rubino P, Zavota L, Bacciu S, et al. (2010) Rituximab ameliorated severe hearing loss in Cogan's syndrome: a case report. Orphanet J Rare Dis 5: 18.
17. Fricker M, Baumann F, Wermelinger F (2007) A novel therapeutic option in Cogan diseases? TNF-a blockers. Rheumatol Int 27: 493-495.