CASE REPORT

Development of a low grade lymphoma in the mastoid bone in a patient with atypical Cogan’s syndrome: A case report

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ABSTRACT

Cogan’s syndrome is a rare disorder characterized by ocular and audiovestibular manifestations in its typical form and carries a wide variety of atypical manifestations. It is considered as an autoimmune disease. We present the first case in the literature of a 67 year old woman with the development of low grade non-Hodgkin lymphoma (NHL) in the mastoid bone in a pre-existing history of atypical Cogan’s syndrome. The anatomical development of NHL was to a “target” organ of Cogan’s syndrome, which is the inner ear.

Introduction

We present a rare case of the development of low grade non-Hodgkin lymphoma (NHL) in the mastoid bone in a patient with an atypical Cogan’s syndrome without progression of NHL and with symptomatic deterioration of Cogan’s syndrome, responding only to TNF-α modulation.

Case presentation

A 67 year old female Caucasian patient from Greece presented in April 2003 with intermittent fevers up to 38 °C. Two months later she complained for additional persistent headaches, bilateral hearing loss, vertigo, tinnitus, and episodes of ataxia. Audiovestibular manifestations were classified as sensorineural
In September 2003 she was admitted to the hospital where an extensive workup was negative except of a brain MRI which showed a presence of a mass lesion over the right mastoid outgrowth (Fig. 1A and B). She underwent surgical biopsy and histologic evaluation revealed a low grade B-cell non-Hodgkin’s lymphoma (NHL) (ICD10:C85) (Fig. 2A and B). Staging evaluation proved to be of IB. She was managed with six cycles of chlorambucil till June 2004, with complete remission of the malignant lesion.

In April 2005 the patient referred to the ophthalmology department with main complains a severe impairment of visual acuity and ocular pain in both eyes. It is worth mentioning that medical history revealed that the patient had experienced episodes of mild visual disturbances during the last semester of 2003 and throughout 2004 overlooked by her. Quite long intervals between visits for follow up and management occurred because of patient poor compliance. In ophthalmologic examination Snellen visual acuity was found to be 0.2 on the right and 0.3 on the left eye; bilateral panuveitis (anterior chamber reaction and vitritis) along with papilledema and increased intraocular pressure in both eyes was diagnosed. Laboratory workup including intraocular fluid studies with PCR, cultures and flow cytometry was not diagnostic; elevated serum IgG titers against CMV were only found. Investigation for tuberculosis, syphilis and sarcoidosis was also negative. The patient was initially considered as a case of CMV associated uveitis treated with intravitreal injection of ganciclovir, cycloplegics, topical steroids and periocular steroid injections. Patient’s ocular manifestations were markedly improved (Snellen visual acuity: 0.7 in each eye and remission of uveitis signs).

However, audiovestibular and institutional manifestations were gradually deteriorated and in June 2006 she was presented with deafness, arthritis, fever, anemia and skin rash whereas, neither oral aphthous along with genital ulceration were observed nor had been ever reported. Ocular manifestations were still under control. The clinical presentation mainly the audiovestibular and ocular manifestations was indicative of Cogan’s syndrome in its atypical form. Full serum autoimmune profile (including antinuclear antibodies, anti-dsDNA antibodies and c-antineutrophil cytoplasmic antibodies) and infectious profile were negative, except for the presence of an IgG monoclonal protein band as well as for elevated erythrocyte sedimentation rate and C-reactive protein levels.

Due mainly to the continuous clinical deterioration of fever, fatigue, headache, skin rash and arthralgias led in November 2007 to the re-administration of chlorambucil and methylprednisolone for another six cycles. During the administration of methylprednisolone skin rash, fever and fatigue got better, only for a short period of time. The patient was practically deaf, with mild visual disturbances, fever, fatigue, malaise, symmetric polyarthritis and cutaneous manifestations. A cutaneous lesion biopsy revealed granuloma annulare. Systematic follow up was negative for NHL progression. The patient was managed from December 2008 till January 2009 with two cycles of cyclophosphamide, vincristine and methylprednisolone and from January till February 2009 with two cycles of rituximab without response.

In February 2009 patient’s ocular disturbances recurred with ocular pain and markedly decreased visual acuity (Snellen visual acuity: 0.025 on the right and 0.1 on the left eye). Cytology of aqueous humor demonstrated inflammatory cells with the predominance of lymphocytes, findings suggestive of chronic active inflammation (uveitis). In the absence of progression of NHL disease and given the fact that our patient was getting worse she was administered infliximab, an anti TNF-a agent, as a third line treatment for Cogan’s syndrome and systemic steroids. Ocular pain and visual acuity were improved (Snellen visual acuity: 0.2 on the right and 0.3 on the left eye) and inflammation regressed, while bilateral papilledema was still present (Fig. 3). Audiovestibular, general symptoms and skin manifestations were moderately improved.

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**Fig. 1** (A) Axial T2-weighted scan (TR/4000 ms, TE/250 ms) demonstrating a low signal intensity tissue (white arrowhead) occupying a large part of the right mastoid. Mastoiditis at the periphery of the lesion appears with high signal intensity (white arrow). The inner ear components appear normal with the expected high signal. (B) Axial contrast enhanced T1-weighted scan (TR/500 ms, TE/20 ms) same level with (A) demonstrates an enhancing tissue (white arrowhead) occupying a large part of the right mastoid. Mastoiditis at the periphery of the lesion appears with intermediate signal intensity (white arrow). No contrast enhancement was observed at the inner ear.
Discussion

In 1945 Cogan’s described a clinical entity which consisted of ocular manifestations of non-syphilitic interstitial keratitis and of audiovestibular manifestations of Meniere-like symptoms. Meniere-like symptoms in Cogan’s syndrome are bilateral, more pronounced, long lasting and may lead to more severe vestibular abnormalities, such as ataxia or oscillopsia. That entity was called after his name and is known till today as Cogan’s syndrome. Later in 1980, Haynes et al. broadened the diagnostic criteria and enclosed other ocular and audiovestibular manifestations and manifestations from other organs, all of which are known as atypical forms of Cogan’s syndrome. Haynes et al. proposed the criteria by which atypical Cogan’s syndrome would be recognized and these include: (1) inflammatory ocular manifestations (episcleritis, scleritis, choroiditis, papilloedema, retinal hemorrhage, retinal artery occlusion, exophthalmos or tendonitis) in the presence or absence of interstitial keratitis, isolated conjunctivitis, subconjunctival hemorrhage or iritis only in combination with Meniere like symptoms within 2 years of symptoms onset, (2) audiovestibular symptoms other than Meniere like manifestations combined with typical ocular manifestations within 2 years of symptoms onset and (3) the presence of typical ocular and audiovestibular manifestations in a period of time more than 2 years between them [1–3].

There are no specific laboratory tests for diagnosing Cogan’s syndrome, except the exclusion of syphilis by serological test. In clinical practice it is sometimes difficult to classify between typical or atypical Cogan’s syndrome, because its physical history may vary considerably. Audiovestibular disturbances can proceed or can appear simultaneously or it may follow ocular manifestations. However, since vestibuloauditory manifestations may precede other symptoms and signs, diagnosis of Cogan’s syndrome should not be overlooked by ophthalmologists in all patients with delayed recurrent ocular inflammation associated with vestibuloauditory symptoms. According to a work of the Study Group for Cogan’s Syndrome [1] ocular and audiovestibular manifestations occurred closely or even simultaneously in most cases with typical Cogan’s syndrome whereas in atypical Cogan’s syndrome the mean interval between the mentioned manifestations was 27.1 months. Table 1 summarizes various signs and symptoms other than ocular and audiovestibular manifestations that can be present, both in typical and in atypical forms of syndrome [1,2]. Although the classification of a patient in typical or atypical Cogan’s syndrome can be misleading, the existing data are not efficient enough to prove that this classification can have an effect on treatment plan or patient outcome.

Cogan’s syndrome is recently being regarded as an autoimmune disorder due to the presence of autoantibodies against the inner ear and endothelium. In mice preclinical models it has
been proved that the intravenous administration of autoantibodies found in patients with Cogan’s syndrome reproduced the classic pathologic manifestations of the syndrome, such as tissue damage of inner ear, endothelial cells and cornea [4].

The association of atypical Cogan’s syndrome with systemic diseases such as rheumatoid arthritis, juvenile arthritis, Sjogren’s syndrome, sarcoidosis, Crohn disease, ulcerative colitis and Wegener’s granulomatosis has also been described and in suspected atypical Cogan’s syndrome investigation aims to rule out systemic lupus erythematosus and Adamantiaiades-Behcet’s disease. In addition, it has been proposed that patients with atypical Cogan’s syndrome may be at higher risk of developing neurological symptoms, lymphadenopathy and splenomegaly [1]. Approximately, 70% of these patients have systemic manifestations, of which vasculitis is considered the pathogenic mechanism and therefore carries a less favorable prognosis than typical Cogan’s syndrome [1,5]. In a retrospective review two patients with Cogan’s syndrome had a history of B-cell lymphoma but in none of them malignancy was developed on the preexisting autoimmune lesion [2]. Recently an atypical Cogan’s syndrome presenting as bilateral endogenous endophthalmitis in a woman with ovarian cancer was reported [6].

The control of symptoms is achieved mainly by the administration of glucocorticosteroids. The most responsive symptoms are the ocular ones (as in our patient), in contrast to the audiovestibular manifestations which are more resistant to therapy. The sooner the steroid administration from the onset of symptoms the better the outcome is. Ocular symptoms are managed quite sufficiently and permanent visual loss has rarely been reported, in contrast to audiovestibular manifestations which after consecutive deterioration usually lead to permanent deafness [1].

After failure of glucocorticosteroids, “second line” therapy is immunosuppressive drugs such as azathioprine, cyclophosphamide, methotrexate and cyclosporine. The best responses have been observed with methotrexate [1,7]. Infliximab might be an alternative therapy for Cogan’s syndrome, especially in cases where corticosteroids and immunosuppressive therapy have failed. Treatment might be more effective when started at an early stage of the inner-ear disease, when the lesions are still reversible [8]. Apart from the administration of the aforementioned agents, surgical interventional techniques such as cochlear implants or hearing aids devices have reported promising results with improved hearing capacity [9–11].

Our patient suffered from atypical form of Cogan’s syndrome and developed B-cell low grade NHL in the mastoid bone. Her NHL responded well to therapy, but Cogan’s syndrome symptoms gradually worsened with the additional cutaneous and institutional manifestations. We speculate that the development of NHL was not accidental, but occurred on the basis of the preexisting immune abnormality and the anatomical distribution of NHL occurred to the organ “target” for Cogan’s syndrome that is the inner ear. In line with this, literature indicates the high risk of NHL development mainly in major autoimmune diseases and the anatomical relationship between them, such as the NHL development in target organs such as glandular parotid in Sjogren’s syndrome [12].

Conclusions

Cogan’s syndrome is a rare clinical entity; infectious and immunological causes have been implicated as triggering factors. Several immune system functional disorders are associated with an increased risk of malignant transformation. As lymphoma is a cancer of the immune system that originates from B and T cells, it seems reasonable that immune dysfunc-

Conflict of interest

The authors have declared no conflict of interest.

Compliance with ethics requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from patient included in the study.

Table 1 Signs and symptoms other than ocular and audiovestibular manifestations in typical and atypical forms of Cogan’s syndrome.

| System          | Manifestations                                                                 |
|-----------------|--------------------------------------------------------------------------------|
| Constitutional  | Fever, malaise, myalgias, headache, fatigue, weight loss                      |
| Gastrointestinal| Abdominal discomfort, mouth ulcers, peptic and colonic ulceration with bleeding|
| Musculoskeletal  | Myalgias, arthritis, arthralgias                                              |
| Cutaneous       | Skin rash, nodules, vitiligo, non-specific urticarial rash, nodules or ulceration of limbs, pyoderma gangrenosum |
| Cardiac findings| Aortic insufficiency, aortitis, cardiomegaly, congestive heart failure         |
| Renal           | Membranoproliferative glomerulonephritis, renal failure                       |
| Vasculitis      | Phlebitis, vasculitis, polyarteritis nodosa, diffuse vasculitis                |
| Nervous         | Central: Meningitis, encephalitis, myelopathy, cerebellar syndrome            |
| Peripheral      | Peripheral: paraesthesia of extremities, trigeminal neuralgia, mononeuritis multiplex |
| Genitourinary   | Mild abnormalities in urinalysis, La Peyronie syndrome with orchitis          |
| Others          | Lymphadenopathy, splenomegaly, hypertension, eosinophilia                     |
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