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CASE BASED REVIEW

Long-lasting uveitis remission and hearing loss recovery after rituximab in Vogt-Koyanagi-Harada disease

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Abstract Vogt-Koyanagi-Harada disease (VKHD) is a multisystemic disorder characterized by granulomatous panuveitis variably combined with T cell-mediated neurologic and cutaneous manifestations. Early and aggressive treatment with systemic corticosteroids is the mainstay of treatment for VKHD. Additional use of immunosuppressants, intravenous immunoglobulins, and tumor necrosis factor-alpha inhibitors can help the most severely affected patients and work as corticosteroid-sparing agents. We report the case of a young woman with relapsing and multiresistant VKHD who demonstrated a stable remission of both uveitis and high-frequency hearing loss following rituximab intravenous administration (1 g. twice, 2 weeks apart, and 6 months later). A complete clinical response was observed 1 month since the first infusion, and no ocular relapses were recorded during the following year; in addition, audiometry showed a high-frequency hearing recovery in the right ear. Further observational studies are required to define the role of CD20 inhibition in the management of VKHD.

Keywords Corticosteroid · Rituximab · Sensorineural deafness · Uveitis · Vogt-Koyanagi-Harada disease

Introduction

Vogt-Koyanagi-Harada disease (VKHD) is a rare T cell-mediated syndrome in which autoimmune reactions are directed against melanin-associated antigens of different tissues, such as the eye, inner ear, meninges, and skin [1]. However, although adaptive immunity has shown to display a key role, the pathogenesis of the disease has not yet been fully clarified [2–5]. Clinically speaking, VKHD onset is characterized by flu-like features and nonspecific ocular signs, often as blurred vision and photophobia (stage 1). Later, patients undergo a progressive granulomatous bilateral panuveitis with exudative retinal detachments variably associated with unilateral or bilateral ear involvement, resulting in progressive sensorineural hearing loss (especially at high frequencies), tinnitus, and vertigo (stage 2). Meningoencephalitis and heterogeneous skin involvement (poliosis, vitiligo, and/or alopecia) can also occur. Stage 3 represents the convalescence stage, which can last from some weeks to several months or be chronic [6]. Therapy in VKHD mainly relies on corticosteroids usually administered as intravenous high-dose pulses (1 g/day of methylprednisolone for 3 to 5 days), followed by high-dose oral prednisone and immunosuppressants and even intravenous immunoglobulins or antitumor necrosis factor-α agents in refractory cases [7].

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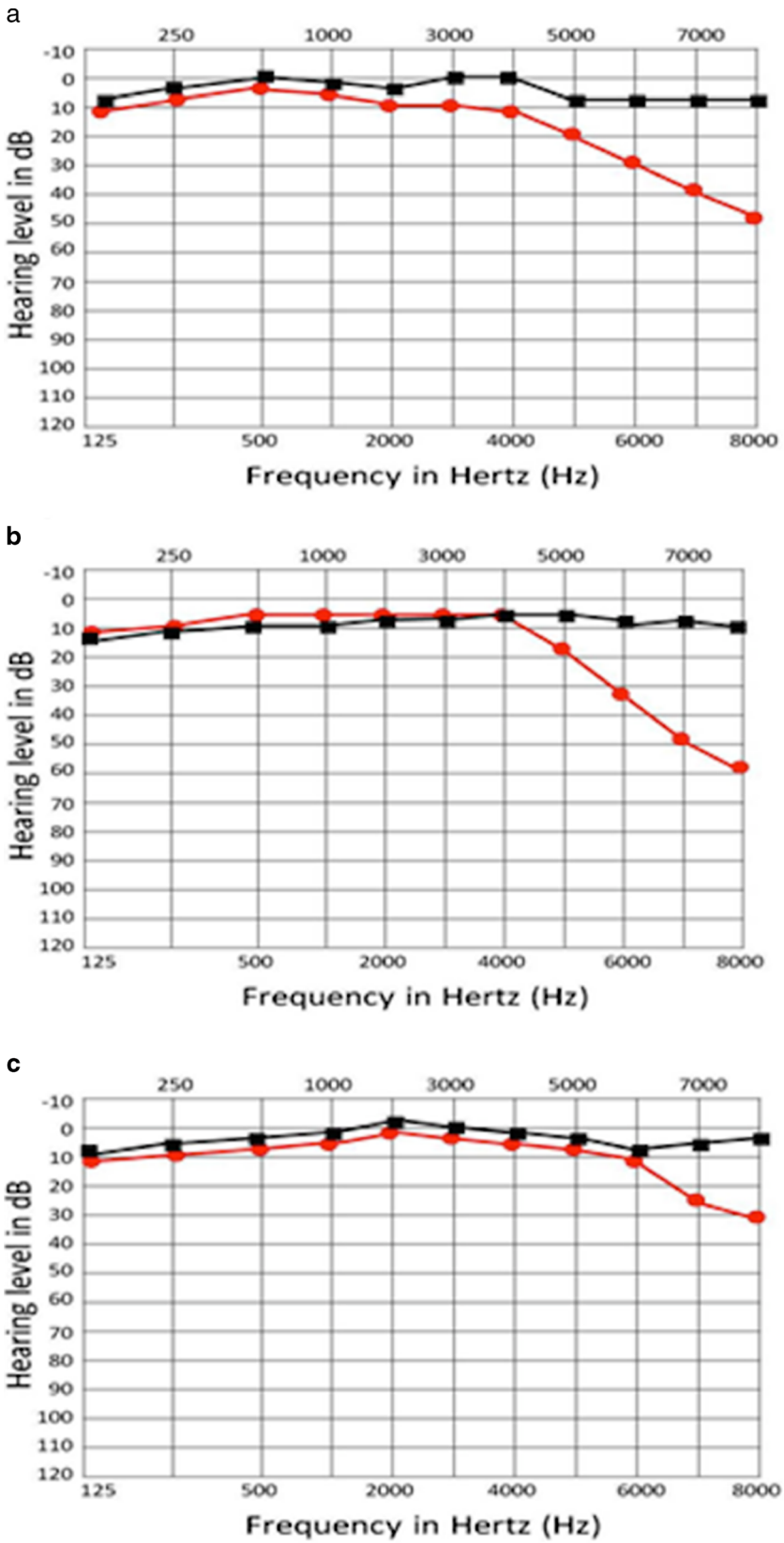

Fig. 1 Audiometry profiles at disease onset (**a**), before the first rituximab infusion (**b**), and after 9 months since the start of rituximab (**c**). Right ear is in *red* and left ear is in *black*. The first two audiograms, **a** and **b**, show a hearing loss of 50 dB and 60 dB, respectively, at 8000 Hz in the right ear. The third audiogram **c** shows a 30 dB loss at 8000 Hz on the right side. *dB* decibel

Case report

We report the case of a 17-year-old woman with a 27-month history of severe multidrug resistant VKHD, who achieved a complete remission after rituximab administration.

At the time of diagnosis, the patient came to our Rheumatology Unit for bilateral blurred vision following a flu-like disease. Later, a progressive eyelash whitening and acute loss of vision due to bilateral granulomatous panuveitis occurred. The patient had previously received cycles of intravenous methylprednisolone (1 g/day for 5 days), followed by 25 mg/day of oral prednisone, topical dexamethasone, and systemic nonsteroidal anti-inflammatory drugs (NSAIDs). Although this treatment brought about a notable improvement within 1 month, a further flare occurred 2 months later, while taking 15 mg prednisolone daily. Our patient referred blurry vision, tinnitus, and hearing loss, with audiometry showing high-frequency sensorineural hearing loss (50 dB at 8000 Hz in the right ear) (Fig. 1a). Therefore, intravenous pulses of methylprednisolone were restarted for 5 days and cyclosporine (150 mg/day) was introduced. We noticed an ocular improvement, but a further flare occurred with bilateral uveitis 1 month later, requiring two intravitreal dexamethasone implants in both eyes [8], which allowed to taper oral prednisone.

After about 2 months, while still on oral prednisone (5 mg daily) and cyclosporine (150 mg/day), the patient complained headache, while severe panuveitis and hearing loss were reconfirmed. Accordingly, audiometry highlighted a further high-frequency sensorineural hearing loss in the right ear (Fig. 1b). For these reasons, the chimeric murine/human anti-CD20 monoclonal antibody rituximab was started at the dosage of 1 g intravenously administered twice, 2 weeks apart, and 6 months later. A complete clinical response was verified within 1 month since the first rituximab infusion, and no relapses were recorded during the following 12 months. In addition, audiometry showed a 30-dB recovery in patient's high-frequency hearing.

Conclusions

This report on a young patient with VKHD complaining panuveitis and unilateral high-frequency hearing loss despite high-dosage corticosteroids and cyclosporine highlights the clinical efficacy shown by rituximab infusions: both ocular and sensorineural auditory remissions were obtained and maintained for a long-lasting time. Rituximab is a chimeric monoclonal antibody against CD20, a specific B cell differentiation membrane antigen, administered intravenously and approved for therapy of lymphomas and rheumatoid arthritis; however, its use has been increasing in recent years for several immune-mediated systemic disorders [9, 10]. To the best of our knowledge, the present report is the second case of VKHD successfully treated with rituximab. Indeed, the first description on its use was reported in a 41-year-old woman with panuveitis and ringing in the ear [5]. Although this patient was refractory to corticosteroids, methotrexate, cyclosporine, adalimumab, and different topic therapies, a fast disease control was obtained after rituximab administration; three additional infusions were subsequently administered after 1, 6, and 16 months, achieving an optimal response without further relapses during 34 months of follow-up. Dolz-Marco et al. stated that changes in B lymphocytes after rituximab therapy could be crucial for changes in T cell trafficking in VKHD [5].

Prognosis of this disabling disorder is mainly based on early diagnosis and targeted therapies. Systemic high-dose corticosteroids and immunosuppressant drugs represent the cornerstone of treatment; however, intravitreal corticosteroids, intravenous immunoglobulins, anti-TNF-α agents (infliximab or adalimumab), and vascular endothelial growth factor inhibitors have also been considered as potential therapeutic choices in refractory cases [1]. Despite VKHD is regarded as a T cell-mediated disorder, also B cells and specific circulating anti-tissue autoantibodies have been reported to be implicated in VKHD pathogenesis [2–5]. Therefore, B cell depletion with rituximab might represent a therapeutic strategy not only in the autoantibody-associated disorders, but also in T cell-mediated diseases, such as rheumatoid arthritis, multiple sclerosis, and also VKHD [11–13]. Further investigations on the role of B lymphocytes in VKHD are needed to explain and establish rituximab's effectiveness in difficult-to-treat patients.

Disclosures None.

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