

Ramsay Hunt Syndrome in a Patient with Ulcerative Colitis Treated with Infliximab

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ABSTRACT

Ramsay Hunt syndrome is a rare complication of herpes zoster that results from reactivation of varicella-zoster virus in the geniculate ganglion of the VII cranial nerve. Immunosuppression can lead to reactivation of latent varicella-zoster virus, resulting in herpes zoster. Here, we present a case of Ramsay Hunt syndrome in a patient with ulcerative colitis under treatment with infliximab.

LEARNING POINTS

- Ramsay Hunt syndrome is a rare form of herpes zoster and characterized by the presence of otalgia, facial palsy, vertigo and vesicular rash in the external ear or on the oropharynx.
- Treatment with TNF inhibitors increases the risk of its development.
- Although not generally recommended, vaccination may reduce the risk of herpes zoster recurrence during TNF inhibitor therapy.

KEYWORDS

Ramsay Hunt syndrome, herpes zoster oticus, ulcerative colitis, infliximab, immunosuppression

INTRODUCTION

Herpes zoster oticus is a viral infection of the inner, middle and external ear characterized by herpetic blisters (small vesicles) of the skin of the external canal and severe otalgia^[1]. These symptoms can be accompanied by vestibulocochlear dysfunction, taste impairment, and dry mouth and eyes^[1]. When herpes zoster oticus is associated with acute peripheral facial palsy, the condition is known as Ramsay Hunt syndrome^[1]. The incidence of Ramsay Hunt syndrome is about five cases per 100,000^[2] and it is characterized by the presence of otalgia, peripheral facial palsy, vertigo and vesicular rash in the external ear or on the oropharynx^[2].

This syndrome is an uncommon cause of otalgia and the second leading cause of non-traumatic peripheral facial palsy^[2]. Ramsay Hunt syndrome is a rare complication of herpes zoster, which results from reactivation of varicella-zoster virus in the geniculate ganglion of the VII cranial nerve^[1]. This condition can also affect other cranial nerves such as the V, VIII, IX and XII, although the VIII cranial nerve is the most frequently involved, along with the facial nerve^[2].

Diagnosis is based on the clinical picture and early diagnosis is extremely important^[1]. In herpes infections, antiviral therapy is most effective when given within 72 hours of symptom onset^[1]. Inflammatory bowel disease is a well-known risk factor for opportunistic infections^[3]. Immunosuppression can trigger reactivation of latent varicella-zoster virus resulting in herpes zoster^[4].

The authors describe a case of Ramsay Hunt syndrome in a 29-year-old man diagnosed with ulcerative colitis and treated with immunomodulators.

CASE DESCRIPTION

A 29-year-old man had been diagnosed with severe ulcerative colitis about 3 months previously and was being treated with infliximab 5 mg/kg, mesalazine 4 g/day, and prednisolone 10 mg/day. He had also iron deficiency anaemia treated with oral iron supplements, and varicella infection during childhood. He had no relevant family history.

The patient was admitted in the emergency department with a 5-day history of right otalgia, the development of vesicles in the right external ear, and vertigo.

Physical examination revealed multiple vesicles in the external ear canal and pain on mobilization of the ipsilateral tragus. Otoscopy was performed, but did not show any changes. Neurological examination showed right peripheral facial paralysis (House-Brackmann grade IV). Further study revealed anaemia (Hb 9.9 g/dl), iron deficiency, and decreased C-reactive protein (1.08 mg/dl; normal <5) (Table 1). Ramsay Hunt syndrome was assumed and the patient was started on intravenous acyclovir 500 mg and methylprednisolone 250 mg. He was discharged with referral for consultation in otolaryngology and rehabilitation.

The patient complete 7 days of therapy with oral acyclovir, topical gentamicin+betamethasone, and oral prednisolone. Currently, he is in a rehabilitation program with significant improvement in facial paresis (grade II–III) and is awaiting audiometric testes. He restarted infliximab after varicella-zoster and herpes PCR tests were negative.

	At baseline
Haemoglobin	9.9 g/dl
Platelet count	200,000/ μ l
Aminotransferase levels	Normal
Coagulation	Normal
Creatinine	0.7 mg/dl
Ac Syphilis, HIV, HBV, HCV	Negative
ANA, anti-DNA ds, ANCA	Negative
Ig, IgA and IgM	Normal levels
C-reactive protein	1.08 mg/dl (<5)
Ferritin	17.9 ng/ml

Table 1. Patient data at baseline

Ac, syphilis screening by ELISA; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; anti-DNA ds, anti-double stranded DNA antibodies; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

DISCUSSION

Ramsay Hunt syndrome is caused by reactivation of latent varicella-zoster virus in the geniculate ganglion (the sensory ganglion of the facial nerve), which affects the VII and VIII cranial nerves because of the close proximity of the facial nerve and the vestibulocochlear nerve^[1]. The subsequent dysfunction of cranial nerves is thought to be caused primarily by viral neuritis and to a lesser extent by inflammatory oedema^[1]. Herpes and varicella-zoster infection affects the thorax in 59% of cases^[5], while herpes zoster affects the head and neck in 45% of cases [5]. Ramsay Hunt syndrome develops in 0.2% of primary herpes zoster infections and mainly affects individuals between 20 and 30 years old, without a gender difference^[6].

Diagnosis is primarily clinical and based on the presence of a combination of severe ear pain, small vesicles in the external canal, and facial palsy^[1]. A high index of suspicion is required when patients present with acute facial weakness, so that the condition can be recognized, timely treatment delivered and the best possible outcome obtained^[1]. Although the appearance of vesicles usually precedes or presents simultaneously with facial paralysis, it may be delayed until facial weakness is clinically evident^[1]. Symptoms and signs of vestibulocochlear dysfunction are not always present but can include hearing loss, tinnitus, vertigo, nystagmus, nausea and vomiting^[1].

In this case, the diagnosis was based on the history, clinical findings, neurological examination and history of varicella infection during childhood. Unfortunately, serum titres of varicella-zoster virus antibodies were not available immediately as serum titres are only useful when the acute and convalescent stages of the condition are being compared.

To objectively describe facial function, the authors use the House-Brackmann facial nerve grading system. This scale ranks facial function in six categories: Grade I - Normal; II - Slight Dysfunction; III - Moderate Dysfunction, IV - Moderate Severe Dysfunction; V - Severe Dysfunction and VI - Total Paralysis^[7]. Inflammatory bowel disease (IBD) is a well-known risk factor for opportunistic infection^[3]. Herpes zoster was one of most frequent opportunistic infections in a cohort of patients followed at the Mayo Clinic^[8]. However, there are few reported cases of Ramsay Hunt syndrome in IBD patients.

Study of a retrospective cohort showed that herpes zoster risk is further increased by the use of corticosteroids, thiopurines and anti-TNF- α therapy^[9]. Recently, JAK inhibitors, which block multiple cytokines via inhibition of the downstream JAK signal, have emerged for IBD treatment^[4]. Therapy with tofacitinib, one of the JAK inhibitors, has been identified independently to increase risk^[10]. Recent in vitro research has demonstrated mechanisms by which tofacitinib reduced interferon- γ production, proliferation, activation, and C-X-C motif chemokine receptor 3 (CXCR3) expression of VZV-specific CD4+T cells^[11].

Infliximab was the first biologic agent for the treatment of IBD and other rheumatic diseases such as rheumatoid arthritis. Serious opportunistic infection and reactivation of pathogens, such as tuberculosis, *Pneumocystis jirovecii*, hepatitis B virus (HBV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV), have been reported to be associated with infliximab treatment^[12]. There are a few cases of Ramsay Hunt syndrome in patients after infliximab treatment. Nagayama et al. reported one case in a patient with rheumatoid arthritis after treatment with infliximab^[13], while Santos-Antunes et al. reported a case in an IBD patient being treated with anti-TNF- α therapy (adalimumab)^[14].

ECCO guidelines state that before starting any biologic therapy, all patients must be asked about any history of chickenpox or shingles [3, 15]. If the history is uncertain or negative, they should be tested for varicella-zoster virus IgG^[3,16].

The risk of herpes zoster could be reduced by vaccination^[4] because the vaccine boosts varicella-zoster virus-specific cell-mediated immunity, thereby controlling the reactivation or replication of the latent virus^[17]. Therefore, vaccination is a potential strategy for reducing the incidence and reactivation of herpes zoster in immunocompromised patients. However, the use of live vaccines, including the zoster vaccine, should be avoided in patients receiving immunosuppressive drugs, because there is a risk of disseminated infection^[3]. ECCO guidelines suggest that seronegative patients should be vaccinated at least 3 weeks before starting immunomodulators^[3]. Furthermore, close monitoring is crucial since herpes zoster is relatively common in these patients and there is a potentially poor outcome in those treated with anti-TNF agents^[3].

Guidelines have been developed for the treatment and prevention of herpes zoster in many immunocompromised situations, but limited information has been published to date regarding the kind of infections, specifically during treatment with biologics^[15].

Varicella-zoster reactivation often has a mild, self-limited course, and does not require discontinuation of immunomodulators or systemic antiviral therapy^[16]. Antiviral therapy is recommended for patients aged over 50 years and also those with moderate to severe pain, severe rash, face or eye involvement, or other systemic complications^[15]. Antiviral therapy is more effective when initiated within 72 hours of the appearance of rash^[15]. In most cases, treatment can consist of oral valacyclovir (1 g three times a day), famciclovir (500 mg three times a day) or acyclovir (800 mg five times a day) for 7 days^[15]. Intravenous acyclovir may be administered for more complicated cases such as disseminated and ophthalmic zoster^[15]. Immunomodulators should not be initiated during active varicella-zoster infection, since it may be exacerbated or even disseminate^[16].

In general, the use of TNF inhibitors such as infliximab should be interrupted at the onset of herpes zoster but can be safely restarted as soon as vesicles have resolved and antiviral therapy has been completed^[15]. There are no universally accepted guidelines for the prevention of herpes zoster during TNF inhibitor therapy^[15]. Routine prophylaxis should be considered for patients with recurrent attacks^[16]. However, the decision to reintroduce anti-TNF therapy and the need for valaciclovir/acyclovir prophylaxis warrants careful consideration on a case-by-case basis^[16]. In our case, the use of infliximab was interrupted but resumed after the patient had negative varicella-zoster and herpes PCR tests.

Early treatment with a combination of antiviral therapy and prednisone is effective for treating Ramsay Hunt syndrome^[18]. Antiviral agents reduce acute pain, improve lesion resolution and prevent postherpetic neuralgia from herpes zoster^[18]. Steroids have a strong anti-inflammatory action, which reduces inflammation and oedema in the nerves involved, which can lead to accelerated recovery of the affected cranial nerves^[18]. Patients with Ramsay Hunt syndrome have poorer recovery than those with Bell's palsy^[19]. Risk factors for a bad outcome include older age, diabetes, delayed treatment and a House-Brackmann grade above IV^[19].

In the case presented, it is assumed that inhibition of TNF- α by infliximab promoted the reactivation of latent varicella-zoster virus in the geniculate ganglion of the facial nerve and caused Ramsay Hunt syndrome. Although it is a rare manifestation of varicella-zoster reactivation, Ramsay Hunt syndrome should be considered in such cases. Our patient received an appropriate diagnosis and started treatment 5 days after syndrome onset, with a good response.

In conclusion, the authors emphasize that prompt diagnosis and therapy may promote a good outcome for this rare condition, even in patients under immunomodulators.

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