



Case Report

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Two multiple sclerosis cases developed herpes zoster during use of fingolimod

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ABSTRACT

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Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system. Immunosuppressive and immunomodulating drugs are used during disease monitoring. Fingolimod is one of the immunomodulatory treatments used in MS patients. It is a therapeutic agent acting on lymphocytes. Latent varicella-zoster virus infections may occur in MS patients receiving fingolimod therapy. In this article, the information of two cases with varicella-zoster virus reactivation during fingolimod use were presented.

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1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system. In patients with relapsing remitting MS (RRMS), immunomodulator and immunosuppressive therapies are administered within certain rules based on the clinical and radiological course of disease. Fingolimod is an oral immunomodulator agent that has been recently started to use. The most commonly observed side effect in patients receiving fingolimod is first-dose bradycardia (Kappos et al., 2010) Lymphocyte counts

of patients may decrease and rarely, lymphopenia may develop. Some opportunistic infections may occur due to decrease in lymphocyte count (Kappos et al., 2010, Cohen et al., 2010).

Varicella-zoster virus is an acute dermatomal viral infection that may cause chickenpox in children and shingles in adults by reactivation of latent virus (Brody and Moyer, 1997). Conditions causing increase in frequency of shingles include decreased cellular immunity and advanced age (Grann and Whitley, 2002). Latent viruses lead to shingles in result of reactivation

either by reinfection or effects of other factors (Cohen et al., 1999). Risk factors for reactivation of zoster include history of varicella, vaccination, age above 50 years, immunocompromised condition, immunosuppressants, chronic steroid administration, AIDS, bone marrow-organ transplantation, cancer, trauma and psychological stress (Bennett 1994; Gnann and Whitley, 2002). In this article, we present two RRMS cases that developed varicella-zoster virus reactivation during the use of fingolimod.

2. Cases

Case 1:

First complaints of a 50-year old woman have been started as weakness in left arm and leg six years ago. Patient was diagnosed with MS due to her attacks as pyramidal involvement repeated within the same year. Treatment with interferon beta was initiated but then, discontinued at the end of 3 years due to frequent attacks of patient and side effects. Patient was followed up without medication for about one year and afterwards, fingolimod therapy was initiated. At the month 6 of this therapy, pain occurred in back and chest of patient, and then rashes were observed (Fig. 1).



Fig. 1. Hyperemic, maculopapulovesicular lesions limited to the midline of a thoracic dermatome.

While white blood cell/lymphocyte counts of patient before fingolimod therapy were detected to be 7.6/1.8 K/ μ L, same counts were found to be 4.5/0.4 K/ μ L during the period that the patient had rashes. Maculo-papulovesicular lesions were observed in dermatologic examination and patient was diagnosed with herpes zoster. Immunomodulator therapy was continued for patient who was in clinical remission period with clinical and radiological fingolimod therapy

and symptomatic treatments were arranged for her complaints. A significant improvement was observed in rashes with these treatments (Fig. 2).



Fig. 2. Hyperemic, macular lesions during recovery.

Case 2:

A 30-year old male patient applied to our clinic with the complaints of weakness in right arm and leg in 2007. Neurological examination revealed loss of strength in right upper and lower extremities, increased deep tendon reflexes in lower extremities and positive Babinski sign in right lower extremity. Patient was diagnosed with MS according to McDonald diagnostic criteria with the neurological examination and cranial MRI images. Attacks of the patient couldn't be controlled under subcutaneous immunomodulatory therapies with the diagnosis of RRMS and oral fingolimod therapy was initiated on February 2012. No new attack was observed in patient during this treatment period. No new and active lesion was detected in cranial MRI imaging. At month 15 of fingolimod therapy, patient applied to our outpatient clinic due to painful rashes at the front left chest and left side of his back which were developed within a few days. History of patient revealed that the rashes have been originated from lower left chest and radiated to the back. Eruption of grouped vesicles upon an erythematous base in a dermatomal distribution which originated from lower left chest and radiated to lower left shoulder blade was observed in examination (Fig. 3). Lesions did not pass the midline and there was no axillary lymphadenopathy. History of patient revealed that he had varicella infection when he was 7 years old. Varicella Zoster IgG was detected to be positive.



Fig. 3. Vesicular lesions on erythematous ground.

Patient was diagnosed with herpes zoster based on his history and clinical findings. Oral fingolimod therapy was continued and symptomatic treatment was initiated for patient and a significant improvement was observed in rashes at week 2 of therapy (Fig. 4).



Fig. 4. Crusted, vesicular lesions during recovery.

3. Discussion

Varicella zoster virus (VZV) belongs to the family of herpes viruses. It usually causes two forms of infection. First one is infectious, benign chickenpox disease of childhood. And the second one is herpes zoster caused by latent virus in dorsal root ganglion (Strauss, 1994). In susceptible people, first pain and then, maculopapular-vesicular lesions occur across dermatome. Particularly, conditions where immune system is

suppressed lead to the risk of herpes zoster (Brody and Moyer, 1997; Grann and Whitley, 2002; Weinberg 2007).

Fingolimod is an immunomodulatory agent that has been recently started to use in MS patients. It acts through sphingosine-1-phosphate receptor which is located at many systems including cardiovascular system, nervous system and immune system (Winkelmann et al., 2012). Release of T lymphocytes from lymph nodes are inhibited resulting in decreased peripheral T lymphocyte counts in patients (Kappos et al., 2010). Thus, increase in opportunistic infections may be observed. Studies with fingolimod have shown an increase in lower respiratory tract infections compared to placebo (Kappos et al., 2010). Two patients have developed primary VZV and herpes simplex encephalitis and prognosis of these patients have resulted in death. It is worthy of note that these patients were in the group of patients receiving high-dose fingolimod (1.25 mg) (Cohen, 2010).

Care must be taken for primary or latent VZV infections in MS patients receiving fingolimod therapy. VZV antibody must be looked for prior to therapy in these patients. If patients have no immunity to VZV, treatment must be initiated after vaccination. For both of our patients, VZV Ig G, which was checked prior to therapy, was found to be positive. Although herpes zoster developed in our patients is common in immunosuppressive patients, it has been very rarely reported in MS patients receiving fingolimod (Uccelli et al., 2011; Winkelmann et al., 2012). Our patients achieved a course without attacks after clinically and radiologically active course due to previous use of injectable immunomodulatory therapies. Oral immunomodulatory drug was not discontinued in our patients as herpes zoster could be controlled with symptomatic treatment and a good clinical response to fingolimod was obtained.

Shingles is diagnosed with classical prodromal pain-burning and shingles rash. Rashes are observed throughout the unilaterally affected dermatome (Bennett, 1994). Cytopathological assessment and polymerase chain reaction may be useful for atypical rashes (Strauss et al., 1994; Weinberg 2007). Virus may stay in lesions occurred for a few days and skin dissemination is not common except for the people whose immune system is suppressed (Strauss 1994). Rashes were painful and at thoracic region in both of our patients. Also in literature, thoracic involvement is observed in 50% of the patients while trigeminal nerve is involved in 10-15% of the patients (Weinberg, 2007). Dermatomes from T3 to L3 are frequently affected (Bennett, 1994). Local pain is severe in shingles.

Frequency of shingles is increased in immunosuppressive patients and recurrence of shingles is observed more frequently in this population

(Weinberg, 2007). History of our cases included use of fingolimod with the diagnosis of MS and these clinical pictures may be observed due to decreased lymphocyte counts because of effect of fingolimod to hold lymphocytes in the lymph node (Ricklin et al., 2013).

Postherpetic neuralgia, ophthalmic involvement and secondary infection of rashes are also important in shingles in addition to severe pain. Postherpetic neuralgia is increased with the age and observed at a rate of 8-70% within a period of 30-60 days (Weinberg, 2007). Initiation of treatment within 3 days of occurrence of rashes ensures a better clinical response in shingles (Dworkin et al., 2007). The aim of the therapy is to ensure rapid improvement, pain control and to reduce the risk of complications as much as possible. Early initiation of antiviral therapy accelerates the healing of rashes, reduce their severity and prevents some complications (Ahmed et al., 2007). Oral treatment is sufficient. Valacyclovir, famciclovir, acyclovir and brivudine may be used in the treatment. However, combined antiviral therapy may reduce the future pain and other complications (Tring et al., 2007). In case of disseminated infection, very severe immune

system suppression and eye involvement, treatment with intravenous acyclovir must be considered if oral uptake is insufficient (Dworkin et al., 2007). Topical antiviral therapy is not relevant. Corticosteroids may only be useful in pain relief when used in combination with antiviral therapy (Dworkin et al., 2007, Ahmed et al., 2007). We also used oral antiviral therapy with the symptomatic treatment for pain in both of our cases and observed a significant improvement in clinical picture within a short period of time.

Fingolimod is a sphingosine-1-phosphate receptor modulator. It is very effective in treatment of multiple sclerosis. However, fatal herpes infections are observed during fingolimod therapy in the literature. Therefore, vaccination is recommended for VZV seronegative patients prior to initiation of fingolimod therapy.

A risk factor for reactivation of zoster is use of an immunosuppressant. Fingolimod, an immunosuppressant, is also important for reactivation of zoster. Therefore, it is important for clinical course of patients to monitor MS patients receiving fingolimod therapy for reactivation of zoster and early initiation of antiviral and symptomatic treatments in case of a potential reactivation.

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