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Aseptic meningitis due to zona zoster infection

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Summary

Zona zoster is generally a benign disease in immunocompetent children. In immunocompromised children, there is a risk of dissemination. Zona zoster rarely causes some neurological complications such as myelitis, aseptic meningitis, encephalitis and ventriculitis in both immunocompetent and immunocompromised children. A 17-year-old girl who had bone marrow transplantation for thalasemia major was admitted to our hospital with fever, itchy rash on the right chest and axillary region and diagnosed as zona zoster. She had severe headache and vomiting on follow-up. Lumbar puncture was performed, because of positive neck stiffness and meningeal irritation signs and pleocytosis and protein elevation were detected in the cerebrospinal fluid (CSF). The diagnosis of aseptic meningitis due to zona zoster was confirmed by VZV-PCR in the CSF. She cured without sequelea after the administration of acyclovir treatment for 10 days. If symptoms such as headache and vomiting develop in immunocompromised children with zona zoster, neurological complications including aseptic meningitis should be remembered. *(Turk Arch Ped 2012; 47: 142-5)*

Key words: Aseptic meningitis, immunocompromised child, zona zoster

Introduction

Varicella zoster virus (VZV) is the cause of chickenpox and zona zoster (ZZ) infection. Primary VZV infection leads to chickenpox. During chickenpox infection, the virus is located in the posterior root ganglions of the spinal nerves and sensory ganglions of the cranial nerves. The virus stays in these ganglions latently for a life time. ZZ develops, when the latent virus activates and reaches the skin in the axon of the sensory nerves and leads to eruption. Increased age and conditions causing depression of cellular immune system are well defined risk factors for activation of the latent virus. Zona zoster infections lead to a benign clinical picture which improves spontaneously in previosly healthy children. However, it may lead to disseminated infection and may be fatal in immunocompromised children. Therefore, acyclovir treatment is used in immunocompromised children with ZZ infection. The disease usually shows a good prognosis also in immunocompromised children with acyclovir treatment (1).

Although zona zoster infections have a good clinical prognosis, they may rarely lead to some complications. These complications include secondary infection on the area of eruption, dissemination of the disease, dysfunction of the involved nerve or disorders caused by lesions in the region innerved by the involved nerve or dissemination of the virus in the central nervous system (2,3). Although it is a well-known and frequent complication after herpes infection in adults, it occurs very rarely in the childhood (1). Central nervous system (CNS) complications which have been reported to be related to zona zoster infection include myelitis, aseptic meningitis, encephalitis and ventriculitis (2,3). In this article, a patient who received bone marrow transplantation 7 months ago because of thalassemia major and who developed meningitis findings during ZZ infection was presented and the related literature was reviewed.

Case

A 17-years-old female patient was presented to our hospital with fever and pruritic eruptions on the anterior surface of the right chest and axilla. Red and pruritic eruptions started on the anterior surface of the chest, high fever, headache and vomiting occured 2 days after the eruptions started. Headache was more severe especially in

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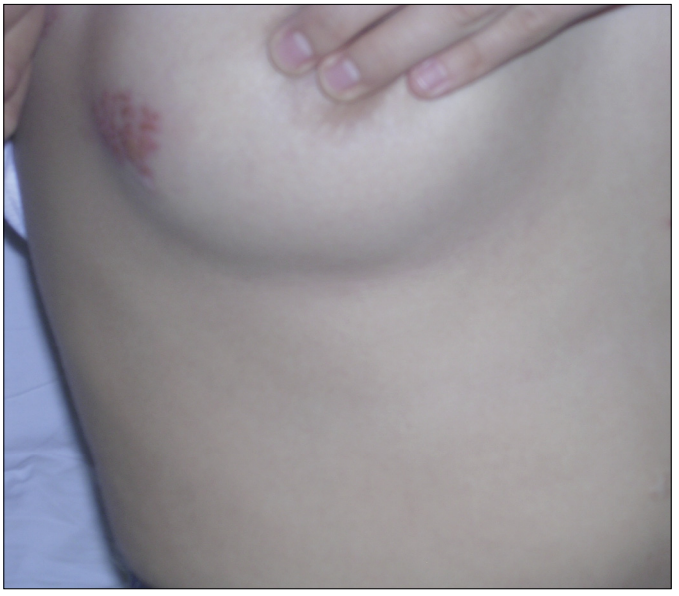
the frontal regions bilaterally. Vomitus contained ingested food and sometimes bile. The patient was diagnosed as thalassemia major at the age of one and recevied fully matched bone marrow transplantation from her sibling 7 months ago. Following bone marrow transplantation fluconasole, trimethoprim-sulphametoxsazole (TMP-SMX) and acyclovir were started for prophylaxis. Cyclosporine A was started as immunosupressive drug. Bone marrow transplantation had a good prognosis and fluconazole was stopped on the 75th day. Acyclovir and cyclosporine A were stopped 20 days before the eruptions started and she was still receiving TMP-SMX. She had chickenpox during her primary school period.

On physical examination, her physical development was compatible with her age. Body temperature was found to be 36.2 °C (axillary), her blood pressure was found to be 110/60 mmHg, her heart rate was found to be 98/min and her respiratory rate was found to be 18/min. Vesicular eruption on an erythematous background compatible with ZZ was observed on the anterior surface of the right chest involving the fourth and fifth thoracal dermatomes and not extending the middle line. Besides the eruption of zona a few vesicular eruptions were present on the anterior surface of the trunk across the middle line (Picture 1). Meningeal irritation findings were suspiciously positive. The other system findings were normal.

Laboratory findings were as follows: hemoglobin 10.6 g/dL, WBC 10 300/mm^3, platelets 350 000/mm^3, erythrocyte sedimentation rate 14 mm/h, C-reactive protein 0.17 mg/dL. Peripheral smear findings were as follows: neutrophiles 50%, lymphocytes 44%, monocytes 4% and bands 2%. Complete urinalysis, renal function tests, hepatic enzymes and electrolytes were found to be within normal limits.



Picture 1. Vesicular eruption in groups developed on an erythemateous background involving the fourth and fifth thoracal dermatomes on the anterior surface of the right chest not extending the middle line and a few vesicular eruptions extending beyond the middle line

With these findings a diagnosis of ZZ infection was made and intravenous acyclovir treatment was started (1500 mg/m^2/day, in three doses), since immunosupression was present. On the follow-up of the patient, it was observed that fever persisted, severe headache was present and vomiting persisted. On the examination performed approximately 8 hours after hospitalization, meningeal irritation findings were found to be positive beyond any doubt. Fundoscopic examination was found to be normal. No abnormal finding was found on neurologic examination except for positive meningeal irritation findings. Lumbar punction was performed considering meningitis. Examination of cerebrospinal fluid (CSF) revealed the following findings: CSF had a clear appearance, cell number 330/mm^3 (lymphocytes 80%, neutrophils 20%), protein 243 mg/dL, glucose 76 mg/dL (simultaneous blood glucose 156 mg/dL). CSF sample was sent for culture. CSF and blood samples were sent for VZV and enterovirus tests and CSF sample was sent for herpes simplex virus (HSV) polymerase chain reaction (PCR) test. According to CSF findings VZV aseptic meningitis was considered and intravenous acyclovir treatment was continued with the same dose. Ibuprophen was started to be administered regularly for headache.

In the clinical follow-up of the patient, high fever, headache and vomiting continued with the same severity for three days. Brain magnetic resonance imaging was found to be normal. CSF culture was found to be negative, CSF and blood VZV PCR were found to be positive, enterovirus PCR was found to be negative and CSF HSV PCR was found to be negative. According to these results a diagnosis of disseminated ZZ and VZV aseptic meningitis was made. After the third day fever started to decrease, headache and vomiting were gradually reduced. On the 6th day of hospitalization fever dropped completely, headache and vomiting improved. Skin lesions started to get crusted during this period. Acyclovir treatment was discontinued on the 10th day, since the clinical findings were improved. On the follow-up visit after one month, she had no complaints and her physical examination was normal.

Discussion

ZZ is a more infrequent disease in the childhood compared to the adulthood. The prevalence increases with increasing age. An important portion of ZZ infections in the childhood is related to conditions and treatments causing immunosupression. Chickenpox infection during the intrauterine period or during the first year of life are established risk factors for occurence of ZZ in the childhood. ZZ infections have a mild course and lead to a clinical picture

which improves in 1-2 weeks in previously healthy children. It may be disseminated and lead to a clinical picture with a fatal prognosis involving multiple organs in previously immunocompromised children. However, it has a good prognosis also in immunocompromised children with early acyclovir treatment.

Various complications related to zona zoster infection may be observed. Secondary infection in the area of eruption, development of disseminated disease and complications related to involvement of the nervous system may be observed. Complications related to the nervous system may occur in relation to dysfunction of the involved nerve or the damage caused by the eruption in the area innerved by that nerve or CNS invasion of the virus (2,4).

Ceratitis and blindness may be observed when ZZ develops in the ophthalmic branch of the trigeminal nevre, osteonecrosis and dental shedding may be observed when the maxillary or mandibular branches of the trigeminal nerve are involved, eruption in the outer ear way and hard palate and facial paralysis (Ramsey Hunt syndrome) may be observed when the facial nerve is involved and ophthalmoplegia, optic neuritis or both may be observed when the occulomotor nerve is involved. During the weeks after zona zoster infection, subgroup cranial nerve paralysis may develop in relation to vasculitis in small vessels. During ZZ infection in the cervical nerves, weakness in the arm may occur rarely (zoster paralysis) and more rarely diaphragmatic paralysis may be observed. During ZZ infection in the lumbosacral nerve, weakness in the leg and sphincter dysfunction in the bladder and intestines may develop rarely (2).

Central nervous system complications related to zona zoster infection are observed more rarely. CNS complications related to ZZ infection include myelitis, aseptic meningitis, encephalitis and ventriculitis (2,4,5). Myelitis and aseptic meningitis are thought to be caused by dissemination of the virus directly into the CNS from the related nerve. The main mechanism of encephalitis is development of vasculitis related to the virus (7). Neurological complications related to zona zoster infection may be observed in the acute phase when eruptions occur or in weeks or months after the lesions are improved (8).

Development of aseptic meningitis during zona zoster infection has been described both in immunocompromised and immunocompetent patients (3,9,10). Aseptic meningitis was also reported to be developed during ZZ infection which occured with vaccine virus (11). Takayama et al. (3) reported that aseptic meningitis developed in 2 of 49 immunocompromised patients (4.3%) with ZZ and in 3 of 45 (6.7%) immunocompetent patients with ZZ in a patient group whom they followed up for 8 years. Meningitis findings may start before the eruption occurs, may be simultaneous with the eruption or may develop in days after the eruption starts (12). Rarely, aseptic meningitis occurs without eruption (13,14). No relation could be found between the area of eruption and development of aseptic meningitis (3). It was reported that Ramsey Hunt syndrome and aseptic meningitis may occur in association (15).

Classical meningitis findings occur in aseptic meningitis accompanying zona zoster infection. Cerebrospinal fluid examination reveals white blood cells with lymphocytic predominance, protein is normal or high and glucose level is normal (4,11,16). In a study performed in 50 immunocompetent adults, pleocytosis was found in 21 subjects (42%) and increased protein was found in 12 subjects (24%), although no clinical finding of myelitis, aseptic meningitis or encephalitis was present in any subject (17). The definite diagnosis is made by demonstrating VZV DNA in CSF by PCR together with clinical findings (18). In the case which we have presented here, eruptions and aseptic meningitis occured simultaneously and CSF examination of the patient was compatible with aseptic meningitis. The diagnosis was made with positive VZV DNA on PCR test of CSF.

Acyclovir is used for treatment of aseptic meningitis accompanying zona zoster infection, but there is no definite consensus about the time of treatment. Generally, treatment for 10 days is recommended (11,12,16,19,20). The prognosis is considerably good with treatment. In the case whom we have presented here, acyclovir treatment was given for 10 days and complete recovery was obtained without any sequelae.

Aseptic meningitis may develop as a rare complication during zona zoster infection both in immunocompromised and immunocompetent children. Frequently, findings of aseptic meningitis accompany skin eruptions. The diagnosis is made by demonstrating VZV DNA by PCR in CSF in presence of clinical findings. The prognosis is considerably good with acyclovir treatment.

References

1. Gershon AA. Varicella-zoster virus. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL (eds). Textbook of pediatric infectious diseases. 5th ed. Philadelphia: Saunders, 2004;1962-71.
2. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med 2000;342:635-45.
3. Takayama N, Yamada H, Kaku H, Minamitani M. Herpes zoster in immunocompetent and immunocompromised Japanese children. Pediatr Int 2000;42:275-9.
4. Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes viruses: herpes simplex and varicella-zoster. Lancet Neurol 2007;6:1015-28.
5. Steiner I, Steiner-Birmanns B, Levin N, Hershko K, Korn-Lubetzki I, Biran I. Spinal cord involvement in uncomplicated herpes zoster. Clin Diagn Lab Immunol 2001;8:850-1.
6. Morgello S, Block GA, Price RW, Petito CK. Varicella-zoster virus leukoencephalitis and cerebral vasculopathy. Arch Pathol Lab Med 1988;112:173-7.
7. Amlie-Lefond C, Kleinschmidt-DeMasters BK, Mahalingam R, Davis LE, Gilden DH. The vasculopathy of varicella-zoster virus encephalitis. Ann Neurol 1995;37:784-90.
8. Gnann JW Jr. Varicella-zoster virus: atypical presentations and unusual complications. J Infect Dis 2002;186 (Suppl 1):S91-8.
9. Lee JH, Kim YS, Suh ES. A case of aseptic meningitis with herpes zoster. J Korean Child Neurol Soc 2005;13:267-70.
10. Kim MA, Yu RM, Kim KH, Chung HJ. A case of acute aseptic meningitis associated with herpes zoster. Korean J Pediatr 2009;52:705-9.

11. Iyer S, Mittal MK, Hodinka RL. Herpes zoster and meningitis resulting from reactivation of varicella vaccine virus in an immunocompetent child. Ann Emerg Med 2009;53:792-5.
12. Mogensen TH, Larsen CS. Aseptic meningitis caused by reactivation of varicella-zoster virus in two immunocompetent patients. Scand J Infect Dis 2006;38:815-8.
13. Jhaveri R, Sankar R, Yazdani S, Cherry JD. Varicella-zoster virus: an overlooked cause of aseptic meningitis. Pediatr Infect Dis J 2003;22:96-7.
14. Mayo DR, Booss J. Varicella zoster-associated neurologic disease without skin lesions. Arch Neurol 1989;46:313-5.
15. Kim JS, Oh CK, Han DK, Yi JS, Woo YJ. A case of Ramsay Hunt Syndrome associated with aseptic meningitis. J Korean Child Neurol Soc 2002;10:362-8.
16. Peña JA, Pirics ML, DiCaprio HS, et al. Varicella reactivation presenting as shingles and aseptic meningitis in an immunocompetent 11-year-old boy. Clin Pediatr (Phila) 2009;48:435-7.
17. Haanpää M, Dastidar P, Weinberg A, et al. CSF and MRI findings in patients with acute herpes zoster. Neurology 1998;51:1405-11.
18. Jeffery KJ, Read SJ, Peto TE, Mayon-White RT, Bangham CR. Diagnosis of viral infections of the central nervous system: clinical interpretation of PCR results. Lancet 1997;349:313-7.
19. Leahy TR, Webb DW, Hoey H, Butler KM. Varicella zoster virus associated acute aseptic meningitis without exanthem in an immunocompetent 14-year-old boy. Pediatr Infect Dis J 2008;27:362-3.
20. Szinnai G, Farron F, Bär G, Heininger U. Herpes zoster and aseptic meningitis in a previously healthy child. Eur J Pediatr 2003;162:434-5.