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CASE REPORT

Meningoencephalitis-Complicating Herpes Zoster Ophthalmicus Infection

Saranya Srinivasan, BS[1]
Grace Ahn, MD[2]
Andy Anderson, MD, MBA[2]

[1] Northwestern University, Feinberg School of Medicine.
[2] NorthShore University HealthSystem.

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Herpes zoster ophthalmicus is a known complication of herpes zoster and the most common manifestation of cranial zoster, accounting for a significant number of zoster cases.[1] An uncommon but serious complication of herpes zoster ophthalmicus is zoster meningoencephalitis. The exact incidence of herpes zoster meningoencephalitis is not known; in 1 series, 5.5% of patients who initially presented with ophthalmic zoster had neurological complications.[2] Here we report a case of herpes zoster meningoencephalitis in a patient with herpes zoster ophthalmicus. ***Journal of Hospital Medicine*** **2009;4:E19–E22.**

KEYWORDS: herpes zoster ophthalmicus, meningoencephalitis, neurological complications, varicella zoster.

Case Report

A 66-year-old woman with a history of breast cancer treated with lumpectomy, chemotherapy, and radiation presented to the emergency department with a 1-week history of left eye pain, progressive fatigue, and numbness and tingling on the left upper face. One week prior to presentation, she experienced dull pain in her left eye, anorexia, vomiting, and numbness and tingling in her upper left face. She was diagnosed with sinusitis by a local physician and prescribed a nasal spray and an unknown antibiotic. She became progressively weaker and fatigued and then 2 days prior to admission she noticed red papules on her forehead. She presented to the emergency department 1 day prior to admission. In the emergency department, she was diagnosed with herpes zoster ophthalmicus, placed on acyclovir, acetaminophen/hydrocodone, ondansetron, and trifluridine eye drops, and discharged. Her symptoms worsened throughout the night and she became progressively more somnolent. She was brought to the emergency department again the following day and was found to be extremely somnolent and oriented only to person. The patient's past medical history was significant for lobular carcinoma in situ of the breast, which was diagnosed 22 years ago and treated with a lumpectomy. She had a recurrence of ductal and lobular carcinoma in-situ 20 years after her initial diagnosis and was treated with 3 months of chemotherapy, completed 13 months prior to admission, and 6 months of radiation therapy, completed 6 months prior to admission. Her physical examination was remarkable for an erythematous maculopapular rash in the distribution of the ophthalmic division of the trigeminal nerve, swelling of the left orbit such that she could not open her eye without assistance, and white mucus-like drainage from the left eye. The area around the eyelid was tender and the left sclera was pink. Extraocular movements were intact and the pupils were equal, round, and reactive to light and accommodation. Cranial nerves III to XII were intact bilaterally; cerebellar function, sensation, proprioception, and deep tendon reflexes were also intact. The patient did not have any meningismus.

On lumbar puncture in the emergency department (ED), the cerebrospinal fluid (CSF) from tube 4 was found to have a glucose concentration of 52 mg/dL (blood glucose of 111 mg/dL), a protein concentration of 90 mg/dL, a red blood cell (RBC) count of 70 cells/mL, and 16 nucleated cells/mL with 67% lymphocytes and 20% monocytes. Viral cultures and polymerase chain reaction (PCR) for herpes simplex virus (HSV)-1, HSV-2, and varicella zoster virus (VZV) were sent to the laboratory. Therapy with acyclovir, vancomycin, and cefotaxime was initiated. Magnetic resonance imaging (MRI) revealed leptomeningeal and dural enhancement involving the posterior fossa, which was read to be consistent with infectious meningitis; temporal lobe involvement was not seen (Figure 1).

Additional results from the lumbar puncture were received the following day. PCR for HSV-1 and HSV-2 was found to be negative, while PCR for VZV was found to be positive. Treatment with intravenous (IV) acyclovir was continued. The patient's clinical condition improved significantly by the morning after admission and she was found to be less somnolent and alert and oriented to person, place, and time. Her condition continued to improve and she was discharged 4 days after admission after her mental status returned to baseline; the patient subsequently completed a 21-day course of 540 mg twice a day IV acyclovir.

In the 9 months following her initial hospitalization, the patient was admitted multiple times to an outside hospital for varicella zoster meningitis and herpes zoster ophthalmicus, with complete resolution of her symptoms after each hospitalization. However, 10 months after her initial

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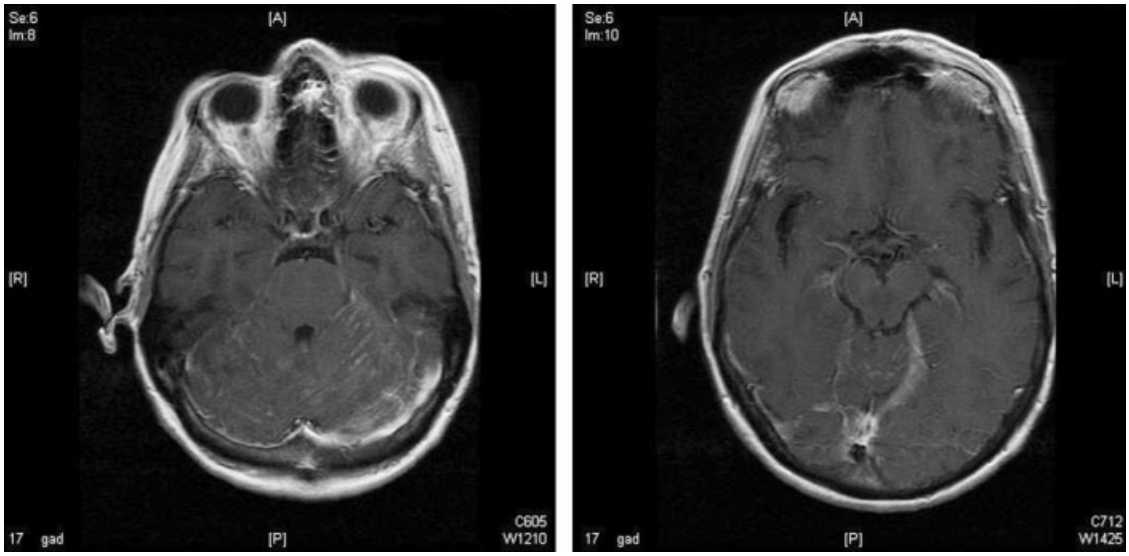

FIGURE 1. Brain MRI with contrast, showing leptomeningeal and dural enhancement in posterior fossa.

hospitalization, the patient presented to our hospital with lethargy and was found to have a recurrence of her breast cancer with metastatic disease. She was subsequently diagnosed with carcinomatous meningitis and passed away shortly after this diagnosis.

Discussion

The development of clinically significant varicella zoster–associated meningoencephalitis after herpes zoster ophthalmicus is rare. Cerebrospinal fluid PCR has been shown to have a sensitivity and specificity >95% for diagnosing VZV encephalitis.[3] The interpretation of the MRI was consistent with several case reports in the literature that also described enhancing meningeal lesions on MRI in patients with varicella encephalitis.[3]

While subclinical invasion of VZV into the central nervous system (CNS) is relatively common, with approximately one-third of asymptomatic immunocompetent patients having a CSF PCR positive for VZV and 46% of patients demonstrating CSF leukocytosis, it is rare for patients to present with the serious clinical manifestations seen in this case.[4] It is hypothesized that herpes zoster–associated meningoencephalitis most likely occurs when the zoster involves the ophthalmic branch of the trigeminal nerve, allowing for the spread of the virus to the tentorium through the recurrent nerve of Arnold, which branches off the ophthalmic division of the trigeminal nerve.[5] On review of the literature, there are very few studies and no controlled trials on the optimal treatment of this complication, although an empirical treatment of 15 to 30 mg of acyclovir per kilogram of body weight for 10 days has been suggested.[3] There have been several reports of rapid responses to IV acyclovir but, due to the rarity of this complication, to our knowledge, no studies have been conducted to determine the optimal treatment of herpes zoster–associated meningoencephalitis.[3,6] A similar case of meningoencephalitis has been described in a 5-year-old boy whose presentation was similar to that of our patient, with periorbital vesicular lesions and mental status changes including somnolence. This child was treated with acyclovir and made a full recovery.[7]

Several other CNS-related manifestations of CN zoster have been reported, including development of the syndrome of inappropriate antidiuretic hormone, development of contralateral hemiparesis, and the coexistence of Ramsay-Hunt syndrome and zoster encephalitis (Table 1). It is hypothesized that stimulation of the ophthalmic division of the trigeminal nerve by the zoster virus leads to excess antidiuretic hormone (ADH) secretion from the posterior pituitary, which results in the development of syndrome of inappropriate secretion of antidiuretic hormone (SIADH). To date, 2 cases of SIADH following a herpes zoster ophthalmicus infection have been reported.[8,9] Several cases of coexisting varicella zoster encephalitis and Ramsay-Hunt syndrome have been reported. Ramsay-Hunt syndrome, which is characterized by zoster oticus and peripheral facial nerve involvement, is a known complication of varicella zoster infection; however, coexistence of Ramsay-Hunt syndrome and varicella encephalitis is rare and has only been reported in 9 patients.[3,10] To our knowledge, the coexistence of these 2 complications has not been reported in a patient with herpes zoster ophthalmicus. Contralateral hemiparesis following herpes zoster infection has been reported in 2 patients, both of whom were treated with acyclovir, resulting in partial recovery. Other CNS complications of herpes zoster include myelitis, large-vessel encephalitis, and small-vessel encephalitis.[3]

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TABLE 1. Clinical Features and Central Nervous System Complications of Ten Patients with Herpes Zoster Ophthalmicus

Report (year)	Age (years), Gender	Presenting Symptom	CNS Complication	Treatment	Outcome
This case	66, female	Vesicles on the left forehead, altered mental status	Varicella zoster meningoencephalitis	IV acyclovir, 540 mg IV q12h, 21-day course	Resolved without complications
Haargaard et al.[2] (2008)	68, female; 82, female; 90, female; 72, male	Unknown	CN III and IV palsies	Systemic acyclovir	Complete recovery in 3 patients, 1 patient with no clinical recovery at 1 month follow-up
	64, female	Unknown	Clinical meningitis (headache, photophobia, neck stiffness) with CSF negative for VZV PCR	IV acyclovir	Complete recovery
	62, female	Unknown	CN III palsy and facial nerve palsy followed by encephalitis	Oral acyclovir 1000 mg Q day followed by IV acyclovir 10 mg/kg TID × 10 days	Minimal recovery with severe neurological and cognitive impairment
Kucukardali et al.[9] (2007)	76, female	Vesicles on left side of forehead	Syndrome of inappropriate antidiuretic hormone	IV acyclovir, 10-12 mg/kg TID for 7 days	Resolved without complications
Dhawan[8] (2006)	71, female	Vesicles on left side of forehead	Syndrome of inappropriate antidiuretic hormone	IV acyclovir, dose unknown	Resolved without complications
Ofek-Shlomai et al.[7] (2005)	5, male	Vesicles on right side of forehead, altered mental status	Varicella zoster meningoencephalitis	IV acyclovir, 1500 mg/m^2/day for 10 days, followed by 14 days of oral acyclovir	Resolved without complications
Ngoueira et al.[13] (2002)	71, male	Recurrent facial rash on right forehead, altered mental status, left hemiparesis	Left hemiparesis, partial palsy of right third CN, complete palsy of left seventh CN with upper motor neuron distribution	IV acyclovir, 21-day course, prednisone short course	Treatment course complicated by renal failure, partial improvement of symptoms with steroids
Hughes et al.[11] (1993)	76, female	Headache, confusion, somnolence, left complete ophthalmoplegia	Meningoencephalitis	Of the 9 patients diagnosed with meningoencephalitis, 5 patients were treated with acyclovir, 3 patients were treated with cytarabine, and 1 patient did not receive any antiviral treatment	4 of the 5 patients treated with acyclovir and the 1 patient who did not receive any antiviral treatment returned to their baseline mental status within 2 weeks. All 3 patients treated with cytarabine and 1 patient treated with acyclovir remained confused and disoriented at 2 weeks and were discharged to care facilities
	74, male	Somnolence, confusion, bilateral Babinski reflexes	Meningoencephalitis		
	69, male	Headache, photophobia, confusion, somnolence	Meningoencephalitis		
	63, female	Headache, blurring of vision, nausea, vomiting, confusion, somnolence	Meningoencephalitis		
McNeil et al.[14] (1991)	51, male	Right hemiparesis, dysphasia	Moderate global dysphasia, right upper motor neuron facial weakness, mild right hemiparesis	Unknown	Progressive improvement of speech, impaired right hand motor function, persistent global weakness

Abbreviations: CN, cranial nerve; CNS, central nervous system; CSF, cerebrospinal fluid; IV, intravenous; PCR, polymerase chain reaction; q12h, every 12 hours; Q, every; TID, three times a day; VZV, varicella zoster virus.

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It has also been shown that patients with compromised immune systems are at a greater risk for recurrence of the herpes zoster infection and for development of zoster encephalitis. It is estimated that mortality rates from zoster encephalitis are as high as 25%, with an average rate of 10%, and are determined by the patient's immune status.[3,4] Our particular patient was immunosuppressed, given that she had been treated for breast cancer with radiation 6 months prior to admission and chemotherapy 13 months prior to admission, putting her at an increased risk of developing encephalitis. There have been reports of herpes-associated meningoencephalitis in patients with systemic cancers, including adenocarcinoma of the lung, prostate cancer, chronic lymphocytic leukemia, and lymphoma; the response to treatment with acyclovir was favorable in these cases.[11] It has also been established that patients with human immunodeficiency virus (HIV) are at increased risk for developing meningoencephalitis after herpes zoster infection as a result of their compromised immune systems.[12] In addition to having a higher mortality rate, patients with compromised immune systems are at a greater risk for recurrence of herpes zoster, which leads to an additional increase in mortality, as was seen in the case of this particular patient.

Address for correspondence and reprint requests:
Dr. Andy Anderson, Department of Medicine, 2650 Ridge Avenue, Evanston, IL 60201; Telephone: 847-570-2509; Fax: 847-570-2905; E-mail: aanderson@northshore.org Received 14 May 2008; revision received 25 October 2008; accepted 29 October 2008.

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