

## Disseminated Herpes Simplex Virus and Varicella Zoster Virus Coinfection in a Patient Taking Thalidomide for Relapsed Multiple Myeloma

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**Disseminated herpes simplex virus (HSV) and varicella zoster virus (VZV) have been reported individually in immunosuppressed adults. We present a case of coinfection with disseminated HSV and VZV infection in a patient taking thalidomide for relapsed multiple myeloma. This is the first report of opportunistic infection associated with thalidomide.**

### CASE REPORT

The patient was a 54-year-old female with a history of hypertension and multiple myeloma diagnosed in 1992, for which she received an autologous bone marrow transplant in 1995. In December of 1999, the patient developed a recurrence of her multiple myeloma, at which time she underwent sacral and left rib radiation therapy and was started on thalidomide therapy at 100 mg/day (which was increased to 200 mg/day 2 months later). She initially presented to an outside hospital with a generalized tonic-clonic seizure, was treated with phenytoin, and underwent a head computed tomography (CT) scan, which revealed a hemorrhage (1.0 by 0.5 cm) in the right putamen. She was immediately transferred to our hospital, where she was found to be obtunded with left-sided hemiparesis. A repeat head CT scan showed a hemorrhagic lesion (4.0 by 3.0 by 4.5 cm) in the right putamen/globus pallidus with slight mass effect and midline shift. Admission laboratory values were significant for a normal international normalized ratio (INR) and partial thromboplastin time (PTT) as well as a normal complete blood count. Liver function tests were not performed on admission, but those done approximately 1 month prior showed an aspartate aminotransferase (AST) level of 23 U/liter, an alanine aminotransferase (ALT) level of 32 U/liter, a total bilirubin level of 0.8 mg/dl, an alkaline phosphatase level of 70 U/liter, and a lactate dehydrogenase (LDH) level of 150 U/liter. She was given one dose of methylprednisolone at 125 mg, and after consultation with the neurosurgical service, conservative medical management was instituted with a nitroprusside drip to keep her systolic blood pressure below 145 mm Hg.

The patient's mental status and neurologic examination were noted to wax and wane over the next few days, prompting two repeat head CT scans, which revealed only a mild increase in surrounding edema and midline shift, but no extension of the hemorrhage. No further steroid therapy was given for the cerebral edema, and she was treated with continued conserva-

tive management. The patient's platelet count was noted to gradually decrease to a minimum of 40,000/mm<sup>3</sup>, which was felt to be related to nitroprusside therapy. She was transfused a total of 48 U of single donor platelets (with two doses of hydrocortisone at 100 mg given with diphenhydramine and acetaminophen to prevent transfusion reaction), and the nitroprusside drip was discontinued with subsequent normalization of the platelet count.

The patient showed some neurological and general improvement until late in the afternoon on the sixth day of hospitalization, when she complained of diffuse abdominal pain. On examination, the abdomen was noted to be distended, tympanitic, and diffusely tender with hypoactive bowel sounds. Flat and upright abdominal plain films with lateral decubitus views showed dilated ascending and transverse colon with gas advancing to the rectosigmoid region consistent with a colonic ileus. Tube feeding was discontinued, and a nasogastric tube was placed for decompression. The patient developed a fever to 38.7°C and became increasingly tachypneic, although her lung exam remained essentially unremarkable. She quickly developed respiratory failure requiring intubation and mechanical ventilation early on day 7 of hospitalization. A chest film revealed new infiltrates in both lung bases, and the patient was started on vancomycin at 1 g every 24 h and piperacillin-tazobactam at 2.25 mg every 8 h for hospital-acquired pneumonia. Liver function tests gave the following results: AST, 1,732 U/liter; ALT, 3,517 U/liter; total bilirubin, 4.2 mg/dl; direct bilirubin, 3.6 mg/dl; alkaline phosphatase, 340 U/liter; LDH, 5,851 U/liter; INR, 2.1; albumin, 2.4 g/dl; amylase, 280 U/liter; and lipase, 365 U/liter. A right upper quadrant ultrasound with Doppler studies revealed a patent portal vein, a narrow but patent inferior vena cava, a homogeneous liver without masses, and a small amount of perisplenic and subhepatic fluid. The patient was then noted to develop a diffuse vesicular rash on her chest, back, and extremities. A Tzanck smear performed on fluid obtained from one of the abdominal wall vesicles revealed numerous multinucleated giant cells consistent with herpes simplex virus (HSV) or varicella zoster virus (VZV). She was started on high-dose acyclovir adjusted for deteriorating renal function for presumed disseminated HSV or VZV (one dose of 5 mg/kg of body weight followed by 2.5

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mg/kg every 24 h), but quickly developed septic shock and expired early on day 8 of hospitalization.

Microbiology results obtained after the patient's death were notable for VZV growing from a culture of an abdominal wall vesicle and HSV-1 growing from an endotracheal tube culture. Of note is that the patient had a positive immune status for VZV infection in 1995 (titer, >1:8). Viral culture taken from an abdominal vesicle punch biopsy was negative, as was one set of viral blood cultures. Sputum culture grew group B streptococcus. One out of four blood culture bottles grew *Candida albicans*. A limited autopsy was performed, with the liver showing extensive necrosis and hemorrhage as well as nuclear changes suggestive of herpes, although in situ hybridization (ISH) results for HSV-1 and -2 were negative. Sections of the lungs also revealed nuclear changes consistent with herpes, and ISH for HSV-1 was positive. Further studies included PCR for HSV, which was positive in the lungs (right and left lower lobes), liver (right and left lobes), and kidneys, confirming disseminated HSV infection.

Despite its previous withdrawal from the market due to severe congenital abnormalities, thalidomide has recently attracted growing interest as a drug with numerous potential therapeutic applications. It appears to be useful in the treatment of diseases such as erythema nodosum leprosum (5), Behcet's syndrome (4), and chronic cutaneous lupus erythematosus (8) and has recently shown promise in the treatment of patients with the wasting syndrome related to HIV (15) and multiple myeloma (14). Despite a growing body of information related to the effects of thalidomide on the immune function, the immunomodulatory and anti-inflammatory properties of this drug remain poorly understood.

Disseminated HSV and VZV have been well described in the adult population. These viral infections occur primarily in patients who are immunosuppressed, with renal transplantation, steroid use, and pregnancy reported as the most frequent causes of impaired immunity (7). As described above, we observed a case of fatal disseminated HSV and VZV coinfection in a patient receiving thalidomide therapy for relapsed multiple myeloma.

**Discussion.** Based on a positive immune status 5 years prior to the time at which she presented with disseminated VZV infection, it is clear that this patient had secondary infection with VZV. In addition, she had evidence of disseminated coinfection with HSV, because PCR studies for this organism were positive in several major organs (lungs, liver, and kidneys). While no specific tests of immune function were performed in this patient to ascertain immunosuppression, we speculate that her overwhelming dual viral infection was related to thalidomide therapy, because no other causes of immunosuppression (such as recurrent multiple myeloma) could be detected.

Several cases of disseminated HSV and VZV have been described in immunocompromised patients, especially in those with defects in cell-mediated immunity. The clinical course of the patient described here (i.e., rapid deterioration leading to multiorgan system failure and death) is similar to that of other patients afflicted with either of these viral infections. However, except for a single previous report of disseminated HSV, dis-

seminated viral infection has never been described in patients with multiple myeloma. Multiple myeloma is predominantly associated with defects in humoral immunity that predispose to bacterial infections (6). Cell-mediated immunity is essentially intact, which accounts for the low frequency of viral infections seen in patients with multiple myeloma (10, 18). In fact, it has been shown that the incidence of recurrent herpes and herpes zoster infections is no greater in patients with multiple myeloma than in healthy individuals (W. L. Morison, Letter, *Lancet* **i**:1293, 1974). To our knowledge, there has been only one case of disseminated HSV in a patient with multiple myeloma reported in the English language literature (2). In that report, the patient was diagnosed with multiple myeloma at the time of HSV infection and had not received any treatment for his multiple myeloma. That patient was also noted to recover spontaneously from his infection with HSV. The reported cause of death was a ruptured diverticulum of the sigmoid colon, and there was no evidence of active HSV infection on postmortem examination.

In the present report, culture of VZV was obtained from one of numerous cutaneous vesicles. In addition, ISH of the lung was positive for HSV-1. The negative ISH in the liver is surprising given the nuclear changes suggestive of HSV noted on autopsy and the positive ISH for this virus in the lungs. Although highly sensitive and specific, ISH has been reported to yield false-negative results in detecting HSV and VZV in lesions showing extensive necrosis (13). In such instances, immunohistochemistry is thought to be more sensitive for the detection of HSV and VZV. However, PCR studies were positive for HSV in several major organs, confirming disseminated infection with this organism. Therefore, the combination of culture, ISH, pathological findings, and PCR studies suggests that this patient suffered from infection with both disseminated HSV and VZV.

Several features of the present case are unique and lead us to believe that immunosuppression from thalidomide therapy may have caused such severe and disseminated viral infection. The patient's overwhelming infection with HSV and VZV occurred almost 5 years after her bone marrow transplantation, well beyond the usual timing for disseminated infection with HSV (20 days posttransplantation) or VZV (45 days to 1 year posttransplantation) (3). Although she received three doses of corticosteroids during her hospitalization, this acute and limited treatment is unlikely to have caused significant immunosuppression.

As mentioned above, there have been numerous studies evaluating the effects of thalidomide on the immune system. For example, thalidomide has been shown to have anti-tumor necrosis factor alpha (TNF- $\alpha$ ) effects both in vitro and in vivo. The role of TNF- $\alpha$  as a key mediator in the host immune response to viral, bacterial, parasitic, and fungal infections has been clearly established experimentally in TNF- $\alpha$  knockout mouse models (1). TNF- $\alpha$  serum levels are increased in diseases such as tuberculosis, human immunodeficiency virus (HIV), and leprosy. Thalidomide selectively inhibits TNF- $\alpha$  secretion from human monocytes stimulated with lipopolysaccharide (17), an effect that occurs through destabilization of TNF- $\alpha$  mRNA (12) and inhibition of Nf- $\kappa$ B activation (9, 11). However, release of other cytokines, such as interleukin-1 (IL-1) and IL-6, is not affected by thalidomide. Thalidomide

also results in significant reduction of levels of TNF- $\alpha$  in serum in patients afflicted with tuberculosis, HIV, and leprosy (16, 19). On the other hand, thalidomide has been shown to mediate stimulation of T-cell proliferation, along with an increase in IL-12 and gamma interferon, through upregulation of CD40L expression. Thus, it appears that thalidomide may have a dual immunomodulatory effect (i.e., downregulation of TNF- $\alpha$  and stimulation of IL-12-secreting T cells) (1). At this time, it remains unclear whether thalidomide has boosting effects on the immune system or, on the contrary, causes immunosuppression that could predispose patients to opportunistic infections. The present case represents the first report of opportunistic infection occurring in a patient receiving thalidomide therapy.

In summary, this case of disseminated VZV and HSV coinfection in a patient with multiple myeloma is unique. We postulate that our patient developed these fatal opportunistic infections as a result of thalidomide therapy. This case should serve to increase awareness of the possible immunosuppressive effects of thalidomide. With the renewed use of thalidomide for treatment of serious conditions such as multiple myeloma and HIV disease, it is likely that similar cases will be encountered in the future.

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