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Case report

Disseminated herpes simplex virus type 1 infection manifested as extensive oral ulcers, pneumonitis, and ileo-colitis in a neutropenic patient post-chemotherapy for osteosarcoma

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ABSTRACT

Herpes simplex virus (HSV) is a common cause of recurrent oropharyngeal ulcers or stomatitis resulting from the reactivation of latent infection since childhood. Extensive ulceration and dissemination to vital organs such as pneumonitis or colitis is mostly encountered among hematologic malignancy or hematologic stem cell transplants. We hereby reported a case with osteosarcoma who developed disseminated HSV infection during neutropenia after chemotherapy.

Background

Herpes simplex virus (HSV) is a double-stranded DNA virus in the herpesviridae family, comprising two species: HSV-1 and HSV-2. Primary HSV-1 infection typically occurs during childhood or early adulthood, manifesting as gingivostomatitis or, often, an asymptomatic infection [1]. The virus's ability to establish latency within a sensory ganglion after primary infection can lead to subsequent reactivation. However, in most cases, HSV-1 reactivation tends to localize within the adjacent organ near where the latent episomes reside, such as in recurrent herpes labialis [1]. Disseminated herpes simplex virus type 1 (HSV-1) infection after local reactivation is typically seen in patients with severe immunosuppression, such as those with hematologic malignancy or hematopoietic stem cell transplant (HSCT) recipients [2]. However, disseminated HSV-1 infection among individuals with solid malignancies is yet reported.

We report a case of disseminated HSV-1 infection involving pneumonitis and ileo-colitis, supplemented with a review of relevant literature.

Case report

A 62-year-old Thai female with osteosarcoma at her left foot was hospitalized due to chemotherapy-induced diarrhea, nausea, and vomiting (CINV) one day after her first cycle of neoadjuvant chemotherapy, which included cisplatin, doxorubicin, and a 4-day course of dexamethasone. She was diagnosed with osteosarcoma (T1N0M0) two months prior, which she presented with pain at her left first metatarsal bone for a year. Before the chemotherapy session, her complete blood count was normal, with hemoglobin of 13.6 g/d, a white blood cell count of 4630 cells/mm^3 (neutrophil 67.2%, lymphocyte 24.8%, with an absolute lymphocyte count (ALC) of 1150 cells/mm^3), and platelet counts of 240,000 cells/mm^3. A complete blood count 3 years prior showed an ALC of 1620 cells/mm^3 (25.9% lymphocytes with a white blood count of 6270 cells/mm^3).

On admission, her symptoms of diarrhea, nausea, and vomiting improved with supportive care. However, she developed a neutropenic fever of 38.3 °C, with white blood cell counts dropping to 390 cells/mm^3. She also had painful perioral and oral ulcers without dysphagia (at rest day 6). She reported self-limited recurrent lips ulceration once to twice a year without a confirmation of etiology. Despite a negative

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Tzanck's smear for multinucleated giant cells, she was treated with acyclovir cream, piperacillin-tazobactam, and granulocyte colony-stimulating factor (G-CSF). On day 9 after chemotherapy, she began to experience dyspnea and hypoxemia. Her white blood count then rose to 19,780 cells/ mm^3, and the G-CSF treatment was stopped. Chest radiography revealed diffuse interstitial infiltration (Fig. 1 A). Multiplex PCR testing for respiratory pathogens from nasopharyngeal swab was positive for coronavirus OC43. Her condition deteriorated with worsening oral ulcers and pneumonitis, which eventually required endotracheal intubation and mechanical ventilation on day 12 post-chemotherapy. Chest CT scans demonstrated diffuse ground-glass opacities and multifocal consolidations compatible with viral pneumonitis (Fig. 1B).

Intravenous acyclovir was administered to treat suspected HSV pneumonitis and stomatitis given her history of undiagnosed self-limited perioral vesicles. A mini-bronchoalveolar lavage (mini-BAL) at the right lower lobe indicated HSV-1 DNA of $>$ 500,000 copies/mL and there were multinucleated giant cells on cytological exam (Fig. 2A). Repeated Tzanck's smear at the lip ulcer site was also positive for multinucleated giant cells (Fig. 2B). Tests for *Pneumocystis jirovecii*, tuberculosis, CMV, bacteria, and fungus from the mini-BAL were all negative. Blood tests for HSV-1 and HSV-2 nucleic acids, conducted after four days of intravenous acyclovir treatment, returned negative results. Unfortunately, it was not possible to get to the leftover serum before the acyclovir treatment for HSV-viral load testing.

Her conditions including fever and oral ulcers improved after four days of intravenous acyclovir, when she underwent successful extubation. However, she later passed the maroon-colored stool. A colonoscopy revealed multiple clean-based ulcers at ileum, cecum, ascending, and descending colon. Pathological examination of ileal and cecal tissue samples showed ulcers with a mix of inflammatory cells. Ballooning cells were observed, characterized by a ground-glass appearance, enlargement, multinucleation, and molding nuclei (Fig. 3 A). These cells tested positive for HSV through immunohistochemistry staining (Fig. 3B). The final diagnosis confirmed a disseminated HSV-1 infection, affecting stomatitis, pneumonitis, and ileo-colitis.

The patient underwent a 3-week course of acyclovir treatment and had an uneventful recovery. Upon discharge, her laboratory investigations showed a white blood cell count of 6140 cells/mm^3 (neutrophils 77.1% and lymphocytes 11.7%). The ALC was 720 cells/mm^3.

The neoadjuvant chemotherapy was discontinued because of this severe complication. She underwent surgical resection of tumor uneventfully 2 months after that. At her one-year follow-up, she reported two episodes of recurrent herpes stomatitis despite being on acyclovir prophylaxis prior to the surgical removal of her tumor. Fortunately, at her 6-month follow-up post-surgery, there were no signs of tumor recurrence, and she also did not have any further episodes of herpes stomatitis. At surgery day, lymphopenia remained a concern, with her ALC at 790 cells/mm^3 (11.7% of a white blood cell count of 6770 cells/mm^3). Her ALC increased from 790 cells/mm^3 at the time of surgery to 1020 cells/mm^3 at 6 months post-surgery and 1800 cells/mm^3 by the 8th month, respectively.

After discussing with the patient, the decision was made to cease acyclovir prophylaxis, given the improvement in her clinical and hematological parameters. We opted for close monitoring to ensure early detection of any recurrent symptoms.

Discussions and conclusions

Although very rare, disseminated HSV-1 infection involving both pneumonitis and ileo-colitis can occur in a neutropenic patient receiving chemotherapy and corticosteroids for a solid malignancy. To our knowledge, this is the first report of disseminated HSV-1 infection in an individual with a solid malignancy. In our case, diagnosing HSV-1 pneumonitis proved challenging. We diagnosed HSV-1 pneumonitis based on the progression of oropharyngeal HSV disease, bilateral infiltrations from a computed tomography scan of the lung, HSV cytopathic changes observed in mini-BAL cells, a very high count of HSV-1 DNA ($>$ 500,000 copies/mL), and clinical improvement following acyclovir therapy. Bilateral ground-glass opacity, interlobar septal thickening, and focal consolidation have been described as typical findings in HSV pneumonitis [3]. Focal necrotizing pneumonia is most often found following HSV tracheobronchial disease as a direct extension, differing from hematogenous spreading [2,4]. Additionally, we observed typical pathologic changes and positive immunohistochemistry tests consistent with definitive HSV-1 infection from multiple gastrointestinal sites. Given the clinical features of bilateral pulmonary infiltrates and multifocal ulcers dispersed from the ileum throughout the entire colon, hematogenous spreading of the virus after oropharyngeal reactivation seems the most likely explanation.

However, detection of HSV-1 from lower respiratory tract specimens does not necessarily indicate HSV pneumonitis. Oropharyngeal contamination of reactivated HSV-1 is common when testing for HSV-1 nucleic acids or culture from respiratory tract specimens [4]. Furthermore, direct extension from oropharyngeal reactivation to tracheobronchial trees may yield positive HSV-1 nucleic acids or culture if HSV tracheobronchitis is present [4]. The definitive diagnosis of HSV-1 pneumonitis necessitates a biopsy of the affected lung tissue showing typical HSV cytopathic changes. However, performing such a procedure in critically ill patients may pose greater procedural risks than a therapeutic trial of acyclovir for probable HSV pneumonitis. One prospective study demonstrated that lower respiratory tract specimen HSV DNA exceeding 5 log GEq/mL (genome equivalent per mL of BAL) correlates with increased mortality odds in critically ill patients [5,6]. A positive

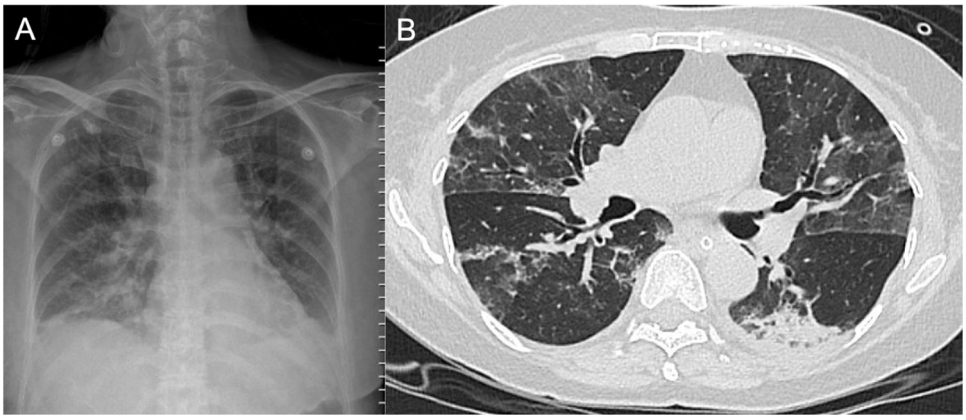

Fig. 1. (1A) Plain chest radiography reveals bilateral opacities predominantly on both lower lung fields and; (2B) an axial view of computed tomography of the chest demonstrates bilateral multifocal bilateral opacities and irregular consolidation at the left lower lung. Diffuse inter- and intra-lobular septal thickening is also seen.

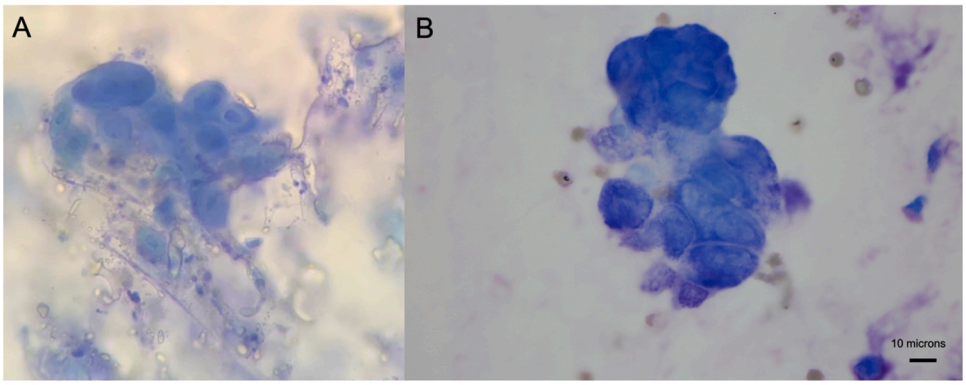

Fig. 2. The figure stained with Wright-Giemsa demonstrates the multinucleated giant cells from (2 A) lips and (2B) mini-BAL, 1000X magnification.

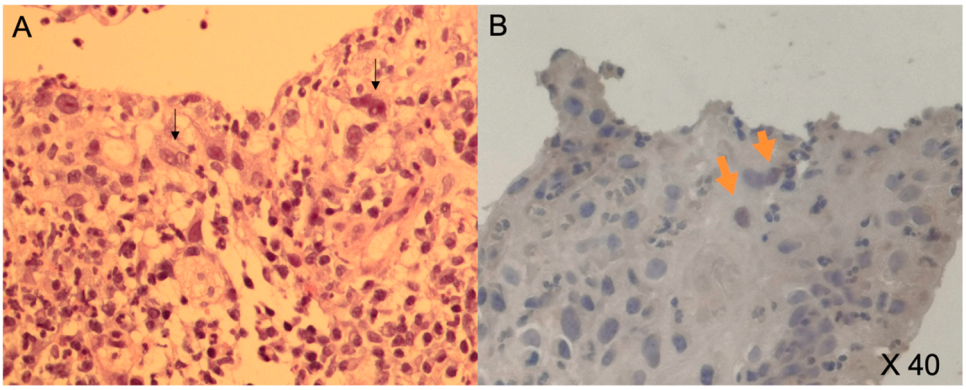

Fig. 3. (3A) The figure from hematoxylin and eosin stain shows typical cytopathic changes related to HSV infection including nuclear molding, margination, and multinucleation with the ground-glass appearance in the nucleus (small arrow); (3B) The cells with cytopathic changes are stained positive for specific immunohistochemistry for HSV (large arrow), 400X magnification.

plasma HSV nucleic acid test can also support a probable HSV pneumonitis diagnosis given the compatible clinical syndrome since contamination or tracheobronchial HSV infection should not yield positive HSV nucleic acid from the plasma. Unfortunately, in our case, the nucleic acid test for HSV DNA in the plasma was conducted post-acyclovir treatment, resulting in a negative outcome.

Considering the presentation, our patient's clinical symptoms, including fever, dyspnea, rales, and preceding mucocutaneous disease, align with previous cohorts of HSV pneumonitis in hematologic malignancies. However, in another cohort exclusively comprising patients with solid malignancies, mucocutaneous disease occurred in only 11% of those with HSV pneumonitis [7].

Classical potential risk factors for HSV pneumonitis include hematologic malignancies, particularly those who have undergone a hematopoietic stem cell transplant (HSCT) [2]. These risk factors were identified from a landmark pathological study that confirmed HSV pneumonitis through histopathological examinations, HSV culture, and molecular methods involving 20 individuals. Notably, 85% had hematologic malignancies, and 80% of these underwent HSCT. Of these patients, 80% received chemotherapy or immunosuppressive therapy, and 60% had either used corticosteroids, experienced neutropenia, or undergone total body irradiation. Only 5% (1 case) had a solid malignancy (rhabdomyosarcoma) in this cohort [2].

Given the rarity of HSV pneumonitis in solid malignancies, we searched PubMed and identified relevant studies, including a retrospective cohort and a case report [7,8]. In a large retrospective cohort comprising 45 individuals with solid malignancies not on acyclovir prophylaxis and suspected of having HSV pneumonitis, only 13.3% had confirmed HSV pneumonitis. Confirmed cases met the criteria of clinical and radiological findings consistent with viral pulmonary infection and a positive HSV culture along with cytopathic changes in cells from the same lower respiratory tract specimens. Importantly, all but one of the confirmed cases (83%) received antiviral therapy targeting HSV. No fatalities were reported, but all required mechanical ventilation, a significantly higher rate compared to those with probable or possible HSV pneumonitis (100% vs. 40% and 50%, $p = 0.03$) [7].

Among confirmed cases, lung and gastrointestinal cancers were the most prevalent, each accounting for 33%. Sarcoma was observed in 17% of cases. Risk factors in these confirmed cases included corticosteroid use (17%) and chemotherapy (50%). Interestingly, all cases exhibited lymphopenia, defined as lymphocyte counts below 1000 cells/mm^3. In contrast, only 17% had neutropenia. This deviates from patterns seen in hematologic malignancy patients, where more cases involve neutropenia coupled with corticosteroid use [2,7].

Although innate and adaptive immunity primarily fend off the virus during initial infections, cellular immunity precursors, especially CD8 + cytotoxic T-cells, are vital for controlling and eliminating reactivated viruses [1,4]. Chemotherapy and the specific type of tumor can also impact lymphocytes [9]. Lymphopenia occurs in up to 3% of individuals with localized tumors like breast cancer and sarcoma, and up to 20% in those with advanced or metastatic solid tumors [9]. Furthermore, certain chemotherapy regimens, including those based on cisplatin, as well as cyclophosphamide, taxanes, and methotrexate, are known lymphopenia inducers [9]. In our patient, lymphopenia was observed both before and after chemotherapy. Lymphocyte counts increased following tumor removal. This suggests that the sarcoma may have quantitatively affected lymphocytes, although the underlying mechanisms remain to be elucidated.

Another case report highlighted both cytologically and molecularly confirmed HSV-1 tracheobronchitis and pneumonitis in a patient with

metastatic small-cell lung cancer who had lymphopenia [8]. This patient had received moderate to high doses of corticosteroids for cerebral edema caused by metastasis and had previously been treated with cisplatin and etoposide. After two cycles of immune checkpoint inhibitors with combined nivolumab and ipilimumab (anti–programmed death 1 agents and anti–cytotoxic T-lymphocyte–associated antigen 4 monoclonal antibody), the patient developed HSV-1 pneumonitis. Currently, neither in-vitro nor clinical data suggest that immune checkpoint inhibitors trigger HSV reactivation or progression [10,11]. The case report postulated that the combination of corticosteroids and lymphopenia might have contributed to the onset of HSV pneumonitis.

Considering these findings, lymphopenia seems to be a significant risk factor for HSV reactivation and its progression to conditions such as pneumonitis. Lymphopenia might be a direct consequence of the tumor's effect on lymphocytes or may result from treatment modalities such as chemotherapy. Notably, the National Comprehensive Cancer Network (NCCN) recommends acyclovir prophylaxis for HSV infection among solid malignancy patients undergoing chemotherapy with a history of prior HSV infection [12]. This stands in contrast to the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO), which advises against routine HSV prophylaxis with acyclovir [13]. Both guidelines emphasize the dearth of evidence supporting or opposing such therapy. Yet, considering the significant morbidity associated with HSV pneumonitis (with 100% of confirmed cases necessitating mechanical ventilation [7]), there is a potential case for primary acyclovir prophylaxis in high-risk individuals. This might especially apply to those with a history of recurrent HSV stomatitis, pre-existing lymphopenia, or those undergoing treatment with a heightened risk of lymphopenia.

HSV pneumonitis has historically been deemed fatal in immunosuppressed individuals, especially those with hematologic malignancies or those undergoing HSCT. In the absence of antiviral treatment, the mortality rate surpasses 80% in these populations [2,4]. However, even with the introduction of appropriate antiviral therapy, a significant mortality rate of 28% persists among critically ill patients without malignancies [14]. Interestingly, among individuals with solid tumors, no fatalities were reported among those with confirmed HSV pneumonitis in the largest cohort studied, with 83% (5/6) receiving antiviral treatment [7]. A recent case report attributed the mortality to factors linked with the advanced stage of the malignancy and palliative care goals [8]. The mortality rates of 14% and 33% in probable or possible HSV pneumonitis cases, respectively, need careful interpretation due to the absence of definitive evidence confirming HSV pneumonitis and the lack of specific antiviral treatment [7].

Given these statistics, antiviral therapy aimed at HSV is generally advocated for critically ill patients presenting with pulmonary symptoms, provided no other clear etiology is evident and HSV testing from a lower respiratory tract specimen returns positive. This recommendation applies even if a pathologic confirmation of HSV pneumonitis is not available [15]. Although strong clinical data supporting antiviral therapy's impact on survival among individuals with solid tumors and confirmed HSV pneumonitis is scarce, the associated morbidity is notable, with 100% requiring mechanical ventilation. The absence of fatalities in treated cases [7] makes a compelling case for the initiation of antiviral therapy when clinically indicated.

In conclusion, HSV-1 pneumonitis and subsequent dissemination to ileo-colitis can manifest in patients with solid tumors receiving chemotherapy. The primary risk factors appear to be lymphopenia and, potentially, corticosteroid therapy. Considering primary acyclovir prophylaxis might be beneficial, particularly for those with a history suggestive of recurrent HSV stomatitis and those with solid tumors undergoing chemotherapy or corticosteroid therapy at high risk for developing lymphopenia.

Ethical approval

This case report was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

Consent

Written informed consent was obtained from the patient for publication of this case report and. accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Contribution

Samadhi Patamatamkul: writing and editing. Narittee Sukswai: pathological reviewing and writing. Onjira Mangkalamanee: writing and editing. Rongpong Plongla: conceptualizing, editing, and final proofreading.

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None.

CRediT authorship contribution statement

Rongpong Plongla: Conceptualization, Writing – review & editing. **Narittee Sukswai:** Investigation, Writing – review & editing. **Onjira Mangkalamanee:** Writing – review & editing. **Samadhi Patamatamkul:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

We declared no conflicts of interest.

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