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【 CASE REPORT 】

Varicella-zoster Virus Related Pulmonary Granulomas in Which Varicella-zoster Virus DNA Was Demonstrated in a Thoracoscopic Lung Biopsy Specimen

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Abstract:
A 43-year-old man with malignant lymphoma who had been treated with the cyclosphamide, vincrstine, procarbazine, and prednisolone (C-MOPP) regimen was admitted to our hospital with skin eruption. He was diagnosed to have varicella, and treatment with acyclovir and immune globulin was started. Chest computed tomography revealed multiple nodules in the both lung fields. Diagnostic thoracoscopic lung biopsy specimens revealed granuloma formation, and polymerase chain reaction testing revealed the presence of varicella-zoster virus DNA in the granulomatous tissue. It was unusual for the lung nodule in varicella pneumonia to increase in size over time in a patient who had undergone antiviral therapy, while also demonstrating multiple granulomas.

Key words: varicella pneumonia, pulmonary granulomas, malignant lymphoma

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Introduction

The varicella zoster virus (VZV) is an infection that is usually contracted in childhood and subsequently confers lifelong immunity. However, the frequency of complications with varicella pneumonia increases when the initial infection is contracted in adulthood, and an aggravated condition and protracted healing are sometimes observed in accordance with the immune status of the patient (1). There have been few reports of the long-term course of adult varicella pneumonia cases. Therefore, a diagnosis is made in most cases based on the preceding characteristic eruption and an increase in the VZV antibody titers. A pathological examination of VZV pneumonia is usually not done. Varicella pneumonia sometimes causes multiple lung nodules, so differentiation from a metastatic pulmonary tumor is necessary in patients with malignant disease. In VZV infection leading to granulomatous disease, however, chest computed tomography scans have been reported to show multiple tiny nodules (2, 3).

We experienced a case in which varicella developed during chemotherapy for malignant lymphoma, and after subsequent chemotherapy for a few months, the pulmonary lesion decreased in size once before growing again to its former state. To excise the pulmonary lesion of the malignant lymphoma, we finally conducted a thoracoscopic lung biopsy that resulted in the successful detection of VZV-DNA in the biopsy tissue. This made it possible for us to prove that this entity was a granulomatous lesion caused by VZV.

We herein report this case, including the pathological examination findings of a pulmonary nodule biopsy.

Case Report

A 43-year-old man presented to our hospital due to a high fever and eruptions on his body and craniocervical regions. The patient had a history of Hodgkin disease and had been

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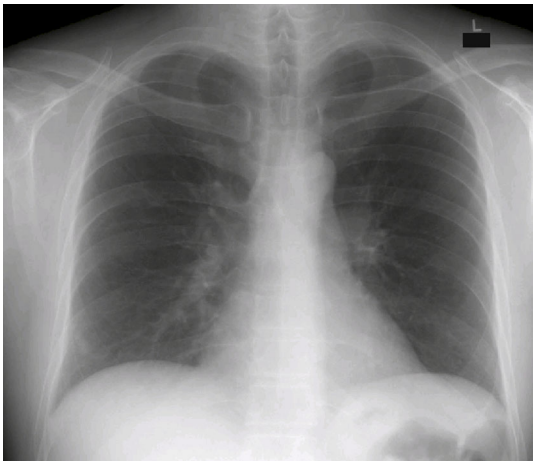

Figure 1. Chest X-ray on admission showing a high density rise in the lower right lung field.

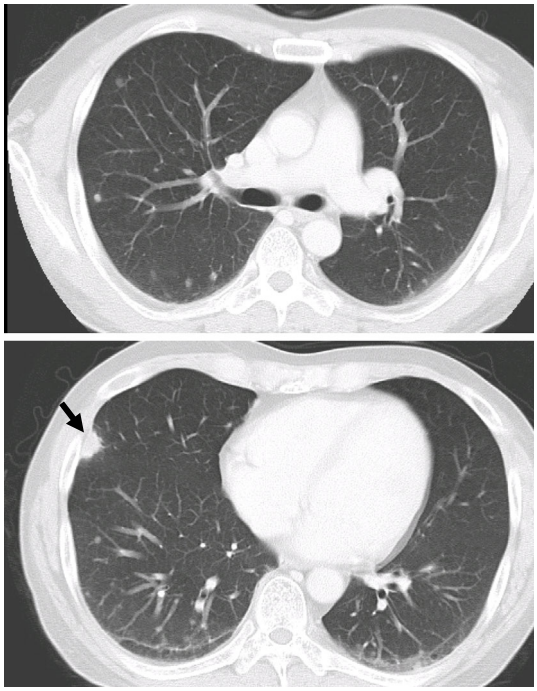

Figure 2. Chest CT showed multiple lung nodules in both lungs except for the right middle lobe nodule (arrow).

treated with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) therapy at our hospital 10 years earlier. Three months prior to this presentation, Hodgkin disease recurred in the right faucial tonsil, and the patient started cyclophosphamide, vincristine, procarbazine, and prednisolone (C-MOPP) therapy. On the 13th day of the fourth course of C-MOPP therapy, he had a high temperature of 39.2℃, a sore throat, and developed eruptions with blistering and crusting on his body and craniocervical regions. Under a suspicion of varicella, he was admitted to our hospital for treatment the same day.

At the time of admission, bullous small eruptions occurred frequently on the face, neck, and precordial region, with some scabbing observed in some other body parts. A laboratory analysis showed a decrease in the white cell count, a decrease in the hemoglobin level, and an increase in the C-reactive protein (CRP) level. We suspected varicella and started the intravenous drip administration of 240 mg of acyclovir 3 times a day from the first day of admission for 7 days, and then added intravenous immunoglobulin (IVIG, 500 mg/kg/day) for 3 days. His eruptions disappeared after approximately three weeks. ELISA for VZV IgG showed a significant elevation from 5.8 cut of index (2nd day after the onset of varicella) to >128 cut of index (17th day after the onset of varicella). The varicella-zoster virus antibody titers (CF) had increased 64-fold (2nd day; 4 versus 17th day; 128 after the onset of varicella). Given the marked increase in both of these serum values, we diagnosed the illness to be a VZV initial infection serologically. He had not suffered from chickenpox in the past and also had not received an inoculation with the chickenpox vaccine.

The patient did not show any respiratory symptoms, and chest radiography on admission showed a nodular shadow in the lower right lung field (Fig. 1). On day fifteen, chest computed tomography (CT) showed multiple lung nodules in both lungs (Fig. 2). Except for the right middle lobe nodule (arrow), each nodule measured from 5-10 mm in size and had a clear and smooth border. No ground glass attenuation was observed around them. We considered these multiple lung nodules to be varicella pneumonia, and differentiation from a metastatic pulmonary tumor from malignant lymphoma was deemed necessary.

On day 36, chest CT showed the right middle lobe nodule (arrow) to have shrunk in size. After administering the 5th and 6th courses of C-MOPP therapy, we performed CT again 5 months after the onset of varicella. The findings showed an increase in the size of the right middle lobe nodule (Fig. 3, 4). At this stage, as the differential diagnosis of lung nodules, viral reactivation after varicella pneumonia, pulmonary infiltration of the malignant lymphoma, and an opportunistic infection after chemotherapy, such as tuberculosis or pulmonary mycosis, were possible.

To determine the optimal treatment, we performed a thoracoscopic lung biopsy of the nodules of the right middle lobe. The pathologic findings showed a large quantity of coagulative necrosis in the central parts and a layer of dense collagen fiber surrounding them. In addition, the nodules had turned into granuloma with the outermost layer covered with epithelioid cells and multinucleated giant cells (Fig. 5).

We noted no atypical lymphocytes in the granulated tissue or any chromosomal aberration of lymphocytes in the areas of granulation. Furthermore, there were no clear fungal images on PAS staining or Grocott staining, and no acid-fast bacilli even on Zeel Neelsen staining. Acid-fast bacilli were also not detected in a culture of the granulated tissue or polymerase chain reaction (PCR). At this point we deemed the nodules most likely to have turned into granulated tissue after VZV pneumonia. By performing PCR of the VZV-DNA in the biopsy specimens, we finally detected VZV-DNA and diagnosed the patient to have developed a granulated lesion

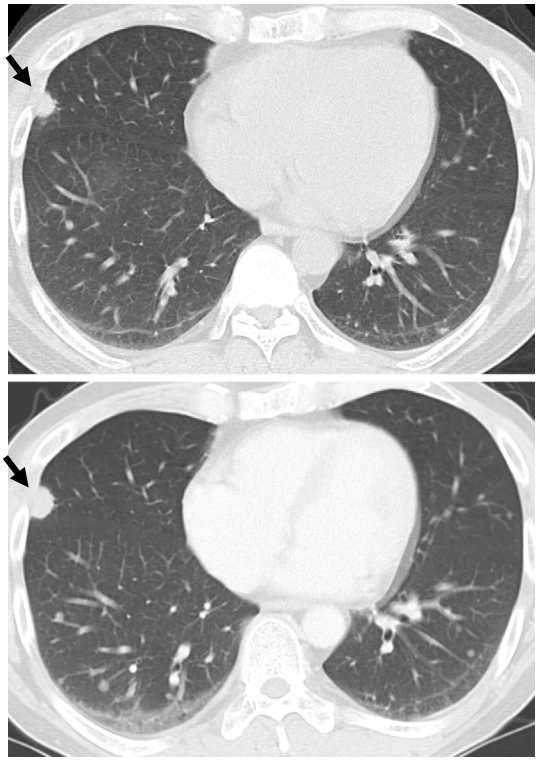

Figure 3. Chest CT on day 36 and five months after the onset of varicella, showing an increase in the size of the right middle lobe nodule (arrow).

after varicella pneumonia.

Discussion

VZV pneumonia is a serious complication of infection with varicella zoster virus, usually presenting as interstitial pneumonitis, most frequently occurring in the periphery of the lung. Such pulmonary involvement may persist for a long time and, very rarely, remains indefinitely as pulumonary nodules of the lungs. However, little is known about the histology and clinical presentation of chickenpox-related granulomas in immunocompetent subjects. The present patient developed varicella during chemotherapy for malignant lymphoma, and frequently occurring nodules persisted in the lung field for a long time. Pulmonary nodules in varicella pneumonia are known to persist for a few months or as long as several years (4, 5). The characteristic finding of our case was that the pulmonary nodules, which showed a shrinking trend even after two courses of chemotherapy had been added for the malignant lymphoma, began to grow again after a period of time off medication. Very few long-term follow-up reports describing pulmonary nodules after varicella pneumonia have been published. In addition, our case is a rare example of pulmonary nodules growing again some time after having initially shrunk in size. To our knowledge, this is the first such case.

Concerning the relapse of the VZV infection in herpes zoster, when NK cells and specific cell-mediated immunity are degraded, viral DNA composition will resume (reactivate), and herpes will develop. However, there have been no reports regarding the mechanism underlying the viral relapse in the granulomatous lesion of varicella pneumonia (6). While it was unclear why the pulmonary nodules, which shrank in size initially, began to grow again in our case. The mechanism of the pulmonary nodules exhibiting a tendency to shrink during chemotherapy despite immunological inhibition after the chemotherapy, continued to inhibit the growth of the virus, by which the healing of the garanulomatous lesion might have progressed. Conversely, the activities of various immune cells that form granulation tissue in response to virus multiplication may have been inhibited by chemotherapy, and as a result, the formation of granulation tissue did not progress.

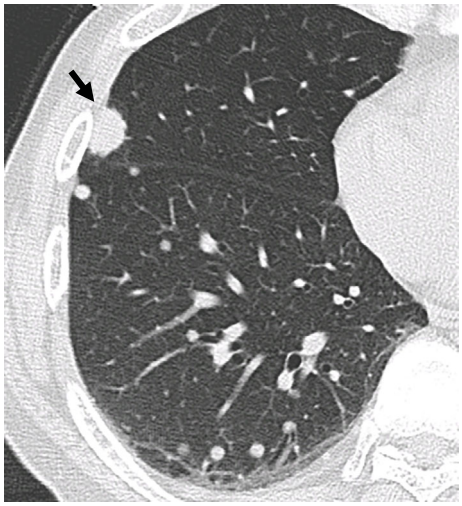

Figure 4. High resolution CT five months after the onset of varicella, showing a well-defined nodule in the right middle lobe nodule (arrow) and well defined, small, randomly distributed, rounded nodules ranging from 3 to 7 mm in diameter.

As for the regrowth of the pulmonary nodules during the withdrawal of chemotherapy, we do not believe it likely that this growth was caused solely by the reactivation of the virus after a sufficient recovery of cell-mediated immunity. The immunocompetent cells whose activity had been inhibited during the chemotherapy may have gradually recovered their normal activity, thereby promoting the formation of granulation tissue.

In the present case, we suspected from the beginning that he was suffering from varicella pneumonia. However, the pulmonary nodules in question were identified not on chest X-ray after the varicella onset but instead by CT performed later. We were therefore not sure whether or not they had been formed soon after the varicella onset.

We ultimately performed thoracoscopic lung biopsy, which proved to be very helpful, and reached a definitive diagnosis of varicella pneumonia. In recent years, as a definitive diagnostic procedure of varicella pneumonia, direct proof of VZV-DNA by PCR has been reported in some reports. Three cases were diagnosed using bronchoalveolar lavage (7), and another was diagnosed using a specimen

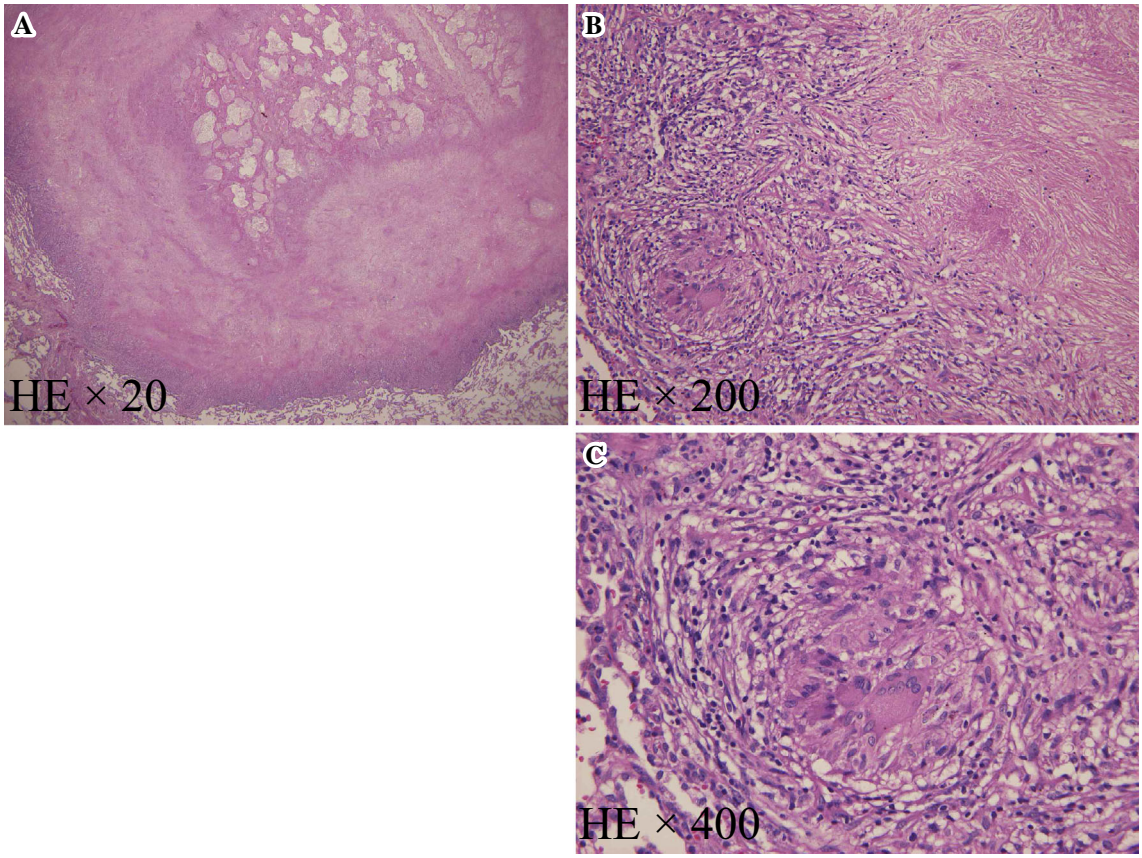

Figure 5. **The pathologic findings showed a large quantity of coagulative necrosis in the central parts and a layer of dense collagen fiber surrounding them [A: Hematoxylin and Eosin (H&E) staining, original magnification ×20]. In addition, the nodules had turned into granuloma with an outer layer covered in epithelioid cells and the multinucleated giant cells (B: H&E staining, original magnification ×200, C: original magnification ×400).**

from a transbronchial lung biopsy; all four cases reached a definitive diagnosis through the direct detection of viral DNA by PCR (8). In addition, specimen collection in all four cases was performed early after the onset, when cutis symptoms were present.

The possibility of DNA detection was relatively unlikely with bronchus washing because it had been several months since the eruption improved, which was the same as in our case. Therefore, a thoracoscopic lung biopsy with a pathological and genetic search seemed to be the most decisive diagnosis technique to adopt in our case. A search of the literature turned up no other reports of the successful detection of VZV-DNA in tissue specimens obtained directly from the nodule lesions after varicella pneumonia.

The incidence of adult varicella pneumonia has differed greatly in reports, ranging from 5% to 50% (9). The symptom of pneumonia develops within 1 to 6 days of the rash onset, often presenting as nothing more than a dry cough. Therefore, many cases of pneumonia, including those with mild symptoms, are often overlooked; however, there have been cases of serious illness or respiratory failure, with a much higher mortality rate in such adults than in infant cases.

The risk factors of varicella pneumonia include pregnancy, smoking, immunologic inhibition, and chronic obstructive pulmonary disease (10). Our patient had multiple risk factors, as he had an immunosuppressed status due to C-MOPP therapy and a high smoking index of 800.

The mechanism of varicella pneumonia is as follows: the entity infects the epithelial cells of the upper respiratory tract and spreads via the lymphatic reticuloendothelial system through regional lymph nodes, causing a transient increase in lymphocytes early in the infection and the onset of giant cells in the reticuloendothelial system. Lymphocytes and monocytes infected with virus are then sprayed into the lungs hematogenously to form pulmonary lesions. The imaging evidence of varicella pneumonia, reflecting the above-mentioned hematogenous dispersal of the virus, tends to show a so-called random distribution without any consistent trend in distribution in the secondary lobule structure. Our patient showed the pattern of so-called hematogenous metastasis, as the nodules were distributed randomly in the lung field, and some of the lesions were observed right under the pleura. Furthermore, the multiple pulmonary nodules of our case were predominantly distributed in the peripheral lungs. However, because there is no basement membrane at the peripheral alveolus level, the virus can easily infiltrate the alveolus epithelium cells directly from the blood vessel

stroma. Necrosis and detachment are noticeable in the alveolus epithelium cells, which may explain the imaging findings mentioned above.

Kim et al. examined cases of varicella pneumonia using high-resolution CT and reported that the nodal size ranged from 1-10 mm in diameter with GGA frequently observed around the node shadow in all cases (4, 5). However, all of the nodules in our case had clear boundaries, and the margins were smooth without GGA. What this GGA pathologically reacts to is unclear at present, but generally speaking, the clinical conditions causing GGA are the stromal infiltration of inflammatory cells, congestion, and intraalveolar imperfect exudative change, which are often found in settings of inflammation around lesions, particularly in the acute phase. In our example, as quite some time had passed after the onset of varicella pneumonia before CT was performed, the formation of the granulomatous lesions was assumed to have been almost completed, with the GGA having already disappeared.

The pathological image of the tissue obtained by a thoracoscopic lung biopsy showed mass coagulative necrosis in the center and a layer of dense collagen fiber surrounding the crust. In addition, the granulomatous lesion itself showed an outer layer surrounded by epithelioid cells and multinucleated giant cells.

Few well-organized reports on histopathology in varicella pneumonia have so far been published. These involved several autopsy cases and reported a small nodular shadow reflecting a bleeding lesion and the focus of necrosis (4). They reported the pathologic characteristics of varicella pneumonia as the onset of fibrinous exudate with the involvement of focal necrosis due to capillary endothelium disorder, mononucleosis infiltration along the alveolar wall, and intraalveolar macrophages (11). These previous descriptions mostly referenced the evaluation of autopsy cases of varicella pneumonia in an acute phase before the formation of granulomatous lesions.

We reported this case as it was unusual for the lung nodules in varicella pneumonia to increase in size over time while the patient was under antiviral therapy, and showing multiple granulomas.

The authors state that they have no Conflict of Interest (COI).

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