Journal of Clinical Virology 56 (2013) 360–364

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Case report

Bronchial ulceration as a prognostic indicator for varicella pneumonia: Case report and systematic literature review

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ARTICLE INFO

Article history:
Received 23 August 2012
Received in revised form 31 October 2012
Accepted 10 December 2012

Keywords:
Varicella zoster
Chickenpox
Pneumonia
Viral
Ulceration
Bronchoscopy

ABSTRACT

Adult varicella pneumonia is a common and serious complication of varicella zoster virus (VZV) infection in pregnant woman and immunocompromised individuals, with mortality rates of 30–50%. The poor prognosis is attributable to very aggressive disease progression and delayed onset of treatment. Here, we present a case of varicella pneumonia in a 69-year-old woman following long-term immunosuppressive treatment for kidney transplant. Respiratory failure developed within 3 d after admission for skin rash, and the patient died 28 d later despite acyclovir and foscarnet treatment. The autopsy showed extensive mucosal airway ulcerations from the pharynx to the main bronchi and numerous VZV-infected cells. We searched PubMed, Web of Science, and EMBASE (1980 through February 2012), as well as several medical report databases created by Japanese healthcare professionals, for all reported cases of varicella pneumonia for which bronchoscopy findings were documented. Twenty-four cases were included and we found that patients with limited or shallow ulcers had favorable outcomes, whereas patients with vast and deep ulcerations had fatal outcomes. These findings indicate that bronchoscopy findings, particularly those showing bronchial involvement, may be useful for evaluating varicella pneumonia.

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1. Why this case is important?

Pneumonia, the most frequent complication of adult varicella often develops insidiously, with mortality rates ranging from 10% to >50%[1] and evolves rapidly; fatality is difficult to avoid once mechanical ventilation is required. Varicella pneumonia is usually detected within 6 d of rash onset and is associated with tachypnea, chest tightness, cough, dyspnea, fever, and occasionally, pleuritic chest pain and hemoptysis. However, these signs appear too late to constitute early biomarkers and are poor indicators of disease severity.[2] Moreover, polymerase chain reaction (PCR)-based diagnosis using bronchial lavage (BAL) for disseminated varicella zoster virus (VZV)[3] infection does not allow early detection, cannot reliably measure disease severity, or serve as a prognostic indicator. Here, we have presented a fatal case of varicella pneumonia in an immunocompromised patient and discussed the relationship between bronchoscopic findings, disease severity, and prognosis.

2. Case description

A 69-year-old Japanese female nonsmoker was admitted to the University of Tokyo Hospital 1 month after kidney transplantation. She had developed end-stage renal failure 20 years earlier due to nephrosclerosis and was being treated with dialysis. She had concomitant hepatitis C and transient atrial fibrillation.

She complained of oral pain and a generalized rash on the day of admission. She had no headache, chest pain, or dyspnea, and her vital signs were stable. Varicella was diagnosed based on cutaneous findings, and 500 mg/d valacyclovir therapy was initiated. However, she developed fever, respiratory failure, and destabilized circulatory dynamics 3 d after admission and was transferred to the intensive care unit. Multiple mouth ulcers were noted, and cutaneous findings showed substantial generalized bullous lesions or pustules with a bright red halo. Mechanical ventilation and cardiovascular management for septic shock were initiated. After mechanical respiration, BAL was performed, and the sample was used for VZV-DNA real time PCR, which yielded positive results (>5.0×10^7 copies/ml; unmeasurable level). Bronchoscopy showed deep ulcerations from the trachea to the bronchi.

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http://dx.doi.org/10.1016/j.jcv.2012.12.013

Infectious disease testing involving electroimmunoluminescence (Seiken, Denka Seiken, Tokyo, Japan) showed that the VZV IgG (0.42; normal value < 0.8) but not IgM levels (10.4; normal value < 2.0) were mildly elevated; these levels increased significantly after 10 d (5.45 and 1330, respectively). In contrast, herpes simplex virus IgM and IgG levels did not increase. Tests for fungi, tuberculosis, and other viruses, including human immunodeficiency virus (HIV), were negative. All initial blood, urine, BAL, and cerebrospinal fluid bacteriological cultures were negative. The viral infection was treated with 250 mg (5 mg/kg body weight) acyclovir and antibiotics. Poor improvement was observed after treatment, and the acyclovir dosage was increased to 500 mg (10 mg/kg body weight) on day 4. Because the patient did not respond to acyclovir until day 10, 1.5 g intravenous foscarnet (30 mg/kg body weight) was administered every 24 h in 1-h infusions. The blood cultures on days 1, 4, and 10 were negative for bacterial infection. The patient's respiratory condition worsened, and she died on day 28. The VZV strain was not determined during the clinical course.

The autopsy showed that the lungs had focal necrosis with a diffuse alveolar damage transition pattern from the leaching to the growth phase and scattered VZV-infected cells. The pharynx and bronchial membranes from the trachea to both bronchi had numerous deep ulcers, and numerous VZV-infected cells were detected microscopically. No other organ showed clear signs of viral infection, although vasculitis was noted in the arteries and veins of the lungs, bladder, and skin.

3. Other similar and contrasting cases in the literature

Our database search, which included PubMed, Web of Science, EMBASE, Japan Medical Abstracts Society, J-STAGE, Medical Online, and CiNii, identified 937 relevant cases. Among these, 915 were excluded based on the following criteria: (1) mixed diagnosis with ulcers that did not clearly point to bronchial ulceration, (2) incomplete or inconclusive diagnosis, (3) incomplete medical history, and (4) availability of only academy meeting abstracts. Twenty-two studies, including twenty-four cases were included in this review: 11 from PubMed, Web of Science, and EMBASE,[4–12] and 13 from the Japanese databases.[13–25] The clinical and bronchoscopic findings, including accompanying diseases and outcomes, are summarized in Table 1. The bronchial findings and chest imaging results obtained from these case reports were examined independently by 3 intensivists (RI, KS, and YA). Diagnoses regarding pleural effusion from all intensivists coincided.

All patients were 24–60 years of age and did not have underlying disease in most cases, although most were smokers. Cough and dyspnea were detected in 12 (50%) and 11 (46%) of the 24 cases, respectively. Two cases had risk factors. Patient 2 had malignant lymphoma but did not take immunosuppressive drugs or steroids in the immediate postremission period.[14] Patient 15 had HIV and received zidovudine, lamivudine, fluconazole, and cotrimoxazole therapy.[9] Only one case increased dose of acyclovir after bronchoscopy.[5]

Bronchoscopy findings were generally characterized by the presence of white-coated tracheal and/or bronchial lesions (first–sixth generation). Detailed analyses suggested that airway lesions appear 1–16 d after the first signs of skin rash, and no relationship was found between the rash's gradual spread over time and disease severity. The patient with the most severe symptoms (#15) had ulcerative and necrotic lesions throughout the bronchi.[9] This HIV-infected patient had recurrent varicella pneumonia and died of acquired immune deficiency syndrome-associated wasting syndrome at 8 months after first admission. These findings suggest that the first lesions are expected to emerge 1 d after the appearance of the skin rash, which may constitute an early diagnostic feature of varicella pneumonia.

4. Discussion and references

Determining the prognosis of adult patients developing pulmonary complications from varicella virus is difficult. Once respiratory distress is diagnosed, the patient's condition generally declines rapidly, providing little time to treat the infection. Here, we have reported the case of an elderly woman who contracted a varicella infection after years of immunosuppressive therapy for kidney transplantation. This therapy may have increased her susceptibility to lung complications. The patient was moved to intensive care for respiratory failure only 3 d after the first signs of skin rash. The natural evolution of VZV infection via an airborne route to the skin conjunctiva and pharynx,[26] followed by postinfection primary viremia that developed 96 h later is consistent with the rapid progression in the current case from skin rash to respiratory failure. This patient died within 1 month despite multiple rescue attempts with well-established treatment regimens. Autopsy showed an unusual pathological feature in the airway, that is, the presence of multiple ulcers from the pharynx to the main bronchi. This rare manifestation motivated us to conduct a literature review to determine whether bronchoscopic findings would shed more light on the early events leading to the untreatable late phase of varicella pneumonia.

Our literature survey showed that adult patients diagnosed with pneumonia varicella are rarely assessed for upper airway pathological features. Over the past 30 years, only 24 cases have adequately documented bronchoscopic findings. All patients with mild respiratory symptoms presented with lesions along the trachea and/or bronchi, generally termed "white-coated lesions."[4,6,9,12,15–24] These lesions consist of endothelial cell damage with focal hemorrhagic necrosis and white-blood cell infiltration into adjacent alveolar walls. All patients who died of respiratory complications from varicella pneumonia were found to have mucosal ulcers in these areas upon autopsy,[27–30] similar to our case. However, several autopsy cases of immunocompromised patients have shown only lung lesions,[30,31] suggesting that nasal, oropharyngeal, or esophageal VZV infections may spread directly to the lungs with the development of vesicular lesions in the trachea of immunocompromised patients, as in our case.

The sequence in which different symptoms of varicella pneumonia evolve must be resolved to identify an early biomarker in order to ensure proper treatment while the patient still has an adequate Acute Physiology and Chronic Health Evaluation score. Bronchoscopy was conducted 1–16 d after skin rash detection in the cases reviewed, although fatal varicella pneumonia has been reported in the absence of upper airway lesions or ulcers.[32,33] Thus, many variables must be considered, including patient age, concomitant lung complications, and inferior care quality, which may cause death before airway lesion development.

Our results suggest that bronchoscopy would be useful for evaluating prognosis. In all 4 cases wherein spirometry was performed upon admission or after therapy, forced expiratory volume in one second and vital capacities were normal, but the diffusing capacity of the lung for carbon monoxide (DLCO) was low.[9,13,15,17] Thus, spirometry may be considered before invasive testing but may be difficult to use as an indication for bronchoscopy because varicella pneumonia affects DLCO. However, the presence of multiple ulcers in our patient's mouth may indicate that VZV erodes the mucosa, including bronchial mucosa, which could indicate the use of bronchoscopy. Although no other cases with oral lesions have been reported in this regard, numerous reports of ulcerative gastrointestinal tract or esophageal tract mucosal lesions were found for fatal cases of varicella.[30,32]

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