Case Reports

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Severe pulmonary co-infection with varicella-zoster virus, *Pneumocystis jirovecii and Cytomegalovirus*: a case report

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Abstract

Pneumocystis jirovecii, *Cytomegalovirus* and varicella-zoster virus are all opportunistically infective pathogens, but pulmonary co-infection with these pathogens is rare. Herein, this case report describes a patient with autoimmune haemolytic anaemia treated with methylprednisolone and cyclosporine that presented with rapidly progressive severe respiratory failure. Analysis of microbial nucleic acid sequences in both blood and sputum using next-generation sequencing revealed pulmonary co-infection with *Pneumocystis jirovecii*, varicella-zoster virus, and possibly *Cytomegalovirus*. After timely targeted and supportive treatments, the patient recovered. This case report highlights the imaging features of co-infection with these pathogens, the importance of next-generation sequencing for early diagnosis in immunosuppressed patients, and the effects of corticosteroid therapy.

Keywords

Cytomegalovirus, next generation sequencing, Pneumocystis jirovecii, varicella-zoster virus

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Introduction

Pneumocystis jirovecii (PJ), *Cytomegalovirus* (CMV) and varicella-zoster virus (VZV) are all common opportunistically infective pathogens of the respiratory tract and a serious health threat for immunocompromised individuals.[1–3] To the best of our knowledge, pulmonary co-infection with PJ, CMV and VZV has not been previously reported. This current case report describes pulmonary co-infection with these three pathogens in a patient with autoimmune haemolytic anaemia, including details on the imaging manifestations, diagnosis and successful therapy.

Case report

In February 2019, a 30-year-old female was brought to the Department of Haematology, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao, Shandong Province, China after experiencing nausea and abdominal pain with a skin rash spread over the body for 7 days. The patient had grain-sized blisters on the arms and the blisters gradually enlarged and spread to the trunk, legs and face with a slight itch (Figure 1a). She had no other complaints, including fever, cough or dyspnoea. She had a history of autoimmune haemolytic anaemia (AHA) for more than 2 years and she was receiving long-term treatment with methylprednisolone and intermittent use of rituximab and cyclosporine for recurrent exacerbation of AHA. She had no personal history of smoking or family hereditary disease.

On admission, there was no obvious rale in the bilateral lungs. The laboratory tests results revealed that CMV immunoglobulin (Ig) M antibody was negative, CMV IgG antibody was positive and 1,3-β-D-glucan and galactomannan levels were slightly increased (Table 1). Computed tomography (CT) of the chest revealed multifocal mixed ground-glass opacities (GGO) from the apex to the bottom of the lung, and from the proximal hilar to the visceral pleura,

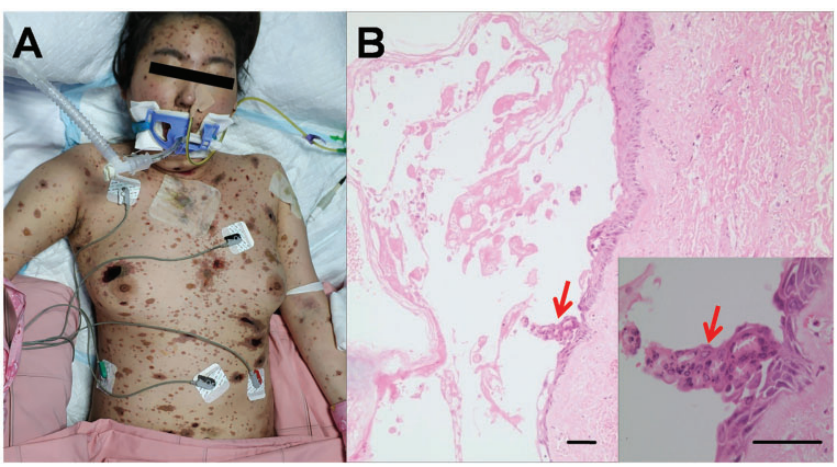

Figure 1. Characteristics of the skin lesions in a 30-year-old female that presented with nausea, abdominal pain and a skin rash that had spread over the body for 7 days: (a) varicella rash on the face, chest and upper limbs; (b) pathology of the skin biopsy showed bullosa formation in the epidermis, dilatation and congestion of intradermal blood vessels, vitreous degeneration of fibrous tissue (scale bar 100 μm) and herpesvirus inclusion body (arrow, scale bar 100 μm). The colour version of this figure is available at: http://imr.sagepub.com.

Table 1. Laboratory parameters on admission and during hospitalization in a 30-year-old female that presented with nausea, abdominal pain and a skin rash that had spread over the body for 7 days.

	Day 1	Day 7	Day 14	Day 21
Physical examination				
New chickenpox	Yes	Yes	No	No
Wet rale	Nothing	A few	Nothing	Nothing
Laboratory tests				
White blood cell, $\times 10^9$/l	3.46	8.78	4.17	2.26
Neutrophils, %	90.8%	94.6%	91.6%	85.0%
CD4+/CD8+ lymphocyte ratio	–	0.18	0.29	–
Haemoglobin, g/l	94	106	82	74
Reticulocytes, %	10.12%	16.1%	–	3.89%
Albumin, g/l	38.0	18.7	31.3	34.2
Total bilirubin, μmol/l	65.8	47.4	19.9	29.4
Unconjugated bilirubin, μmol/l	42.8	14.2	5.7	12.3
LDH, U/l	393	508	478	–
PCT, ng/ml	–	1.12	0.16	–
CMV IgM antibody, U/ml	<5	–	–	<5
CMV IgG antibody, U/ml	114	–	–	132
1,3-β-D-glucan, pg/ml	187	246	193	234
Galactomannan, μg/l	0.7	0.40	0.25	0.38
PaO_2/FiO_2	–	62.5	176	376
CMV nucleic acid detection copy/ml	–	1.70 E3	–	1.51 E3

LDH, lactate dehydrogenase; PCT, procalcitonin; CMV, cytomegalovirus; Ig, immunoglobulin; PaO_2/FiO_2, partial pressure of arterial oxygen/fraction of inspired oxygen ratio.

with a small amount of bilateral pleural effusion (Figure 2, day 2 panel). After admission, 40 mg/day methylprednisolone intravenous and 125 mg/12 h cyclosporine oral were administered to treat the AHA. In view of her immunocompromised situation and the levels of 1,3-β-D-glucan and galactomannan, 400 mg/day moxifloxacin and 200 mg/12 h voriconazole were administered intravenously for the empirical treatment of pneumonia.

The patient gradually developed dyspnoea and her body temperature reached a maximum of 37.5°C. On day 7, the partial pressure of the arterial oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2) was 138. Electronic bronchoscopy revealed oedema of the tracheal wall with local protruding lesions; rough and erosive mucosa was evident after removal of secretions (Figure 3). Bacterial and fungal cultivation tests of bronchoalveolar lavage fluid (BALF) were negative.

On day 8, CT revealed small multifocal ill-defined areas of nodular opacity with the GGO halo sign in both lungs (Figure 2, day 8 panel). The saturation of arterial blood oxygen (SaO_2) decreased to 70% when a non-invasive ventilator was used with an oxygen flow of 6 l/min and positive end expiratory pressure (PEEP) of 6 cmH_2O. Therefore, she was intubated with an oral tracheal cannula and transferred to the intensive care unit. Biphasic positive airway pressure ventilation, continuous sedative analgesia and muscular relaxation therapy were applied. Treatment with moxifloxacin and voriconazole was ceased. Then, 50 mg/day caspofungin, 1000 mg/8 h meropenem, 1000 mg/8 h vancomycin, 500 mg/8 h acyclovir and 500 mg/8 h ganciclovir were administered intravenously to

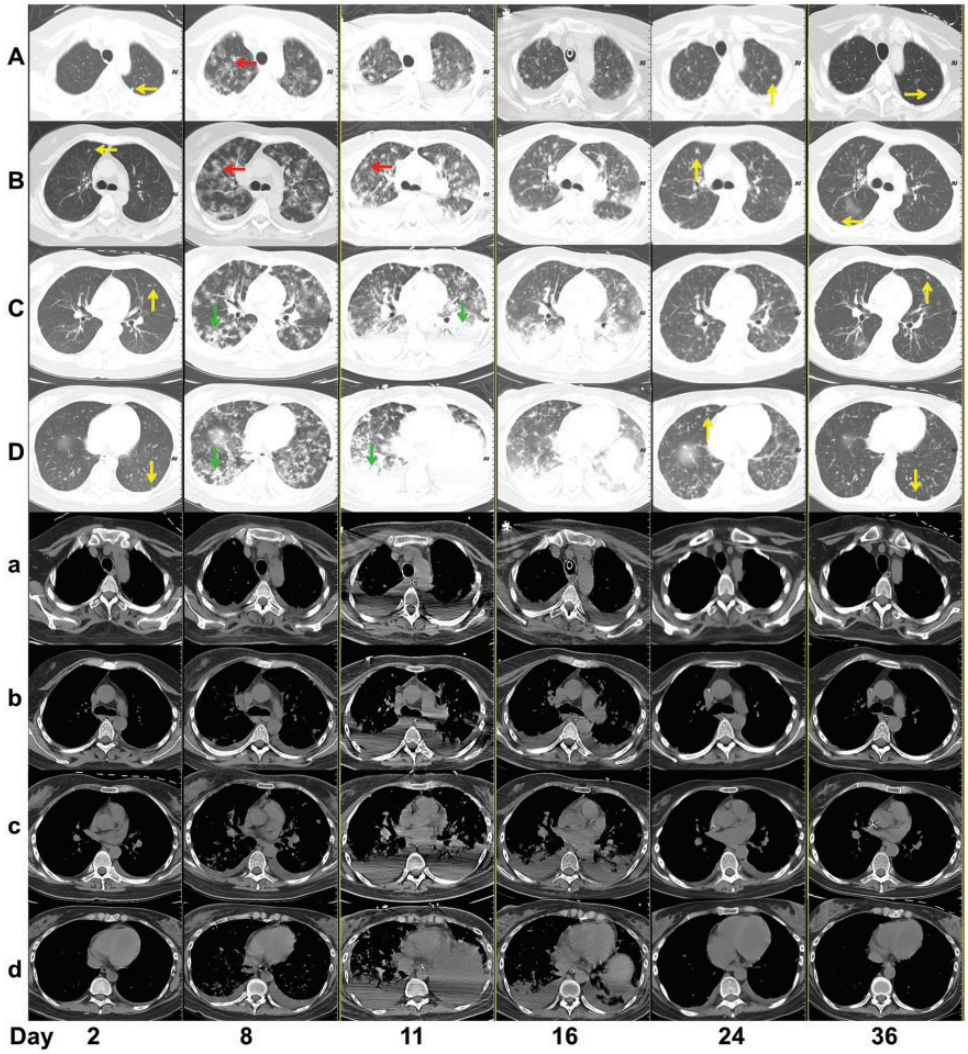

Figure 2. Dynamic evolution of chest computed tomography in a 30-year-old female that presented with nausea, abdominal pain and a skin rash that had spread over the body for 7 days. Lung window (rows A–D): initial imaging demonstrated multifocal nodular opacity with the slightly ground-glass opacity halo sign (yellow arrows) and bilateral pleural effusion (panel day 2). Lesions enlarged and developed to be ill-defined patchy areas (red arrows) and partly merged and formed consolidation (green arrows) (panel day 8, day 11). After effective treatment, ground-glass opacity and consolidation gradually dissolved (panel day 16, day 24) and a few nodular opacities similar to the initial lesions remained (panel day 36). Mediastinal window (rows a–d) showed some non-specific changes such as pleural effusion and compression atelectasis. The colour version of this figure is available at: http://imr.sagepub.com.

cover as many potential pathogens as possible. Meanwhile, pathogen detection in the blood and sputum was performed using next-generation sequencing (NGS).

When the PEEP was adjusted between 10 and 15 cmH_2O and the FiO_2 was adjusted between 70% and 100%, the SaO_2 was difficult to keep at 90%. The lowest

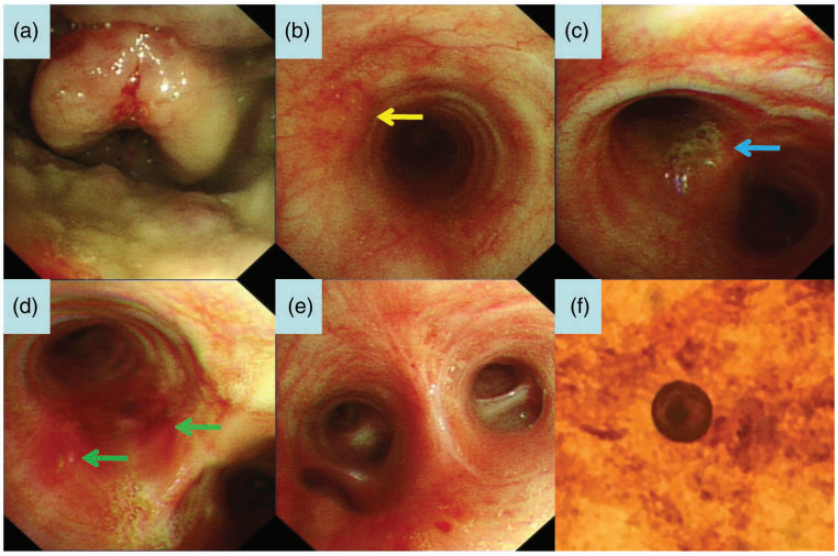

Figure 3. Performance of fibreoptic bronchoscopy in a 30-year-old female that presented with nausea, abdominal pain and a skin rash that had spread over the body for 7 days: (a) epiglottic oedema; (b) trachea wall oedema and local lesions (yellow arrow); (c) phlegm attached to left principal bronchus (blue arrow); (d) mucosal bleeding after clearance of phlegm (green arrow); (e) congestion and oedema of segmental bronchial mucosa; (f) trophozoite in bronchoalveolar lavage by hexamine silver staining. The colour version of this figure is available at: http://imr.sagepub.com.

PaO_2/FiO_2 ratio was 62.5. Prone positioning did not effectively improve oxygenation. Intravenous methylprednisolone was increased to 80 mg/day. Some tests were rechecked: CMV nucleic acid level: $1.70 \times E3$ (reference: $<5 \times E3$), $CD4^+$ lymphocytes: 26/μl, $CD4^+/CD8^+$: 0.18.

On day 11, the PaO_2/FiO_2 gradually increased to 108. CT revealed consolidation (Figure 2, day 11 panel). NGS performed on both blood and sputum detected PJ, CMZ and VZV nucleotide sequences. Skin biopsy revealed viral inclusion bodies (Figure 1B), which confirmed varicella caused by the herpes virus. Caspofungin and vancomycin treatment was ceased. Then, 240 mg/1200 mg/6 h trimethoprim-sulfamethoxazole (TMP-SMX) oral combined with 500 mg/8 h acyclovir and 500 mg/8 h ganciclovir administered intravenously were used to treat the mixed infection. According to the NGS results, hexamine silver staining of BALF was undertaken and the staining of trophozoites further confirmed PJ infection. The PaO_2/FiO_2 gradually increased. Intravenous methylprednisolone was decreased to 40 mg/day after 5 days of 80 mg/day.

On day 16, CT revealed improvement of the lung lesions. The oral tracheal cannula was removed and the patient was transferred back to the Department of Haematology. On day 36, CT revealed that the inflammatory exudation was mostly absorbed, but scattered mixed GGO was still present. TMP-SMX was adjusted to 160 mg/800 mg/day oral for preventive therapy. The ganciclovir was continued until day 42 and the acyclovir was continued until day 69.

Discussion

This current case report presents a patient that had severe pneumonia caused by PJ,

VZV and CMV. To the best of our knowledge, this is the first report on this co-infection in the literature. Diffuse mixed GGO nodules, which rapidly enlarged and fused, were important imaging changes, accompanied by lung consolidation and pleural effusion. Routine pathogen tests were not sufficiently sensitive and NGS was important for early aetiological diagnosis. Timely targeted therapy and corticosteroid pulse treatment were beneficial for the patient's outcome.

Opportunistic infections, including PJ, are found increasingly in non-human immunodeficiency virus (non-HIV) patients.[1] PJ is usually concomitant with CMZ infection.[1] Combined therapy using corticosteroids and other immunosuppressants may be a risk factor for CMV co-infection among patients with PJ pneumonia.[1] This AHA patient had a long history of recurrent methylprednisolone and cyclosporine therapy, which increased the probability of this co-infection. VZV pneumonia is also prone to occur in immunosuppressed patients.[4] Therefore, for patients that have a history of immunosuppressive therapy or immunosuppressive diseases, a mixed infection should be considered when severe atypical pneumonia occurs.

Pneumonia has different imaging characteristics for different pathogens. For PJ, the most frequent finding is symmetrical, apically perihilar distributed GGO with peripheral sparing.[5] Centrilobular nodules, a crazy-paving appearance and nodules are the most common manifestations of CMV infection.[6] Nodules distributed in multilobar segments are a typical image feature of varicella pneumonia.[4] PJ and CMV infections can show similarities in GGO, while CMV and VZV infections share similarities in centrilobular nodules. This case was characterized by diffusely distributed centrilobular nodules, GGO with rapid progress and fusion, so it was difficult to analyse for a specific pathogen. In addition, bronchoscopy revealed local protruded lesions in the trachea and main bronchus. Rare cases in the literature have reported white-coated protruded lesions in the trachea and bilateral bronchi in VZV pneumonia; patients with limited or shallow bronchial ulcers had favourable prognoses.[2] The current patient was initially treated with empirical antibacterial, antifungal, anti-CMV and anti-VZV therapies. However, the therapeutic response was not good, which indicated that the empirical therapy was wrong or did not adequately cover the aetiological pathogens. The patient presented a severe and progressive respiratory failure. Oxygenation was hard to maintain despite bundle therapy that included positive-pressure ventilation, prone positioning, continuous sedation and analgesia, and muscle relaxation.

Routine pathogen tests were undertaken, including sputum culturing, blood culturing and detection of pathogenic antibodies. However, no positive results were found. NGS on the sputum and blood was performed and aetiological results were obtained within 48 h. Compared with traditional tests, NGS is not limited by specific mediums or culture methods, can perform 'pan-viral' and 'pan-microbial' screening, and shows a good diagnostic value for various pathogens, including PJ, CMV, and VZV.[7–9] It is especially superior for detecting specific pathogens in a mixed infection.[10] In theory, NGS specificity is increased by using combined blood and lower-respiratory-tract samples, such as BALF and sputum. The clinical manifestations, imaging characteristics, high nucleic acid levels detected in both blood and sputum and the therapy responses all supported VZV and PJ infection in the current case. Detection of trophozoites in BALF using hexamine silver staining further confirmed PJ infection. A diagnosis of CMV infection cannot be confirmed by clinical manifestations and CT imaging. However,

PJ infection is often accompanied by CMV infection.[1] Since CMV nucleotide sequences were detected in both the blood and sputum, it was necessary for us to be alert to CMV infection. According to these results, targeted therapies were performed and the pneumonia was relieved rapidly and effectively.

In addition to routine anti-pathogen drugs, a corticosteroid pulse was administered for this current patient. Corticosteroid therapy for pneumonia is controversial and it may have different effects in pneumonias caused by different pathogens. In a few case reports and a non-strict retrospective case–control study on VZV pneumonia, treatment with corticosteroids showed a much more rapid improvement in oxygenation and a trend towards shortening the duration of mechanical ventilation.[3] However, another study revealed that patients treated with corticosteroids had longer mechanical ventilation durations and similar hospital mortality.[4] Thus, the effect of corticosteroids remains uncertain. The routine adjunctive use of corticosteroids in non-HIV patients with PJ pneumonia and respiratory failure is not recommended.[11] Moreover, it remains unclear how to treat these patients (maintaining the dose versus escalation versus tapering). For CMV pneumonia, corticosteroid therapy suppresses the CMV-specific T-cell immune responses.[12] Therefore, corticosteroid treatment should not be administered to patients with CMV pneumonia.

In this current case, due to progressive AHA, methylprednisolone and cyclosporine were administered. In view of the continuously deteriorating PaO_2/FiO_2 ratio, methylprednisolone was doubled to 80 mg/day as an antivirus and anti-PJ treatment. The PaO_2/FiO_2 improved rapidly. This suggests that VZV pneumonia dominated the severe respiratory failure. Therefore, corticosteroid therapy should be considered for VZV pneumonia patients with severe respiratory failure. In the future, randomized controlled trials will be necessary to determine the efficacy of corticosteroid treatments in non-HIV patients with VZV and PJ pneumonia.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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