Abstract:
A 72-year-old woman with rheumatoid arthritis was treated with methotrexate (MTX) and iguratimod. Upon examination of a liver tumor, blisters due to varicella-zoster virus (VZV) infection were observed. Despite oral administration of valacyclovir, she developed varicella pneumonia and meningoencephalitis. A VZV antibody test revealed reinfection. The liver tumor shrank after discontinuance of MTX, and polymerase chain reaction revealed the reactivation of the Epstein-Barr virus (EBV). Therefore, we were unable to deny MTX-associated lymphoproliferative disorder (MTX-LPD). This is the first case of a complication of pneumonia and meningoencephalitis due to VZV reinfection and EBV reactivation.

Key words: varicella, pneumonia, meningoencephalitis, rheumatoid arthritis, Epstein-Barr virus

(Intern Med 61: 2961-2965, 2022)
(DOI: 10.2169/internalmedicine.8413-21)

Introduction
Varicella, an infection caused by the varicella-zoster virus (VZV), generally develops in childhood, and most cases have a mild clinical course. However, VZV latently infects the human sensory nerve ganglia after treatment of varicella. When the host’s immune system is weakened, VZV reacti-vates, and herpes zoster occurs (1). In addition, cases of VZV reinfection in adults have been reported even if they have an antibody against VZV. The rate of reinfection is reportedly higher in immunocompromised hosts than in healthy individuals (2). An adult varicella surveillance study reported that 21% of 1,047 patients with VZV infection were reinfected (3).

VZV infections in adult patients are known to cause pneumonia, hepatitis, and encephalitis, among others, unlike in children, in whom VZV infections are less severe (4). In addition, eight cases complicated by pneumonia and central nervous system infection have been reported in previous studies (5-12). The modes of infection in these cases were reported to be reactivation in four cases, primary infection in one case, and VZV reinfection in one case; however, the modes of infection in the remaining cases were not reported.

We herein report a case of severe pneumonia and meningoencephalitis due to VZV reinfection during immunosuppressive treatment for rheumatoid arthritis (RA). Furthermore, our case was complicated by Epstein-Barr virus (EBV) reactivation. This is the first case of VZV reinfection and EBV reactivation in a patient with RA who was treated
A 72-year-old woman had been treated for RA with methotrexate (MTX) (6 mg/week) and iguratimod (25 mg/day) for the past 6 years. Her serum hepatic enzyme level had been elevated three months prior, and abdominal contrast computed tomography (CT) revealed a liver tumor. Therefore, she was admitted to our hospital for a further examination. Upon admission, she presented with multiple painless blisters on the whole body and mucosal lesions from the oral cavity to the throat. She had not had any contact with varicella patients but had a history of varicella and had not received the VZV vaccine. In addition, the test for VZV-IgM was negative, and VZV-IgG titer detected through enzyme immunoassay was 27.9. Based on these observations, we determined her infection to have a pre-infection pattern. In contrast, the Tzanck test of the vesicles was positive. Thus, she was diagnosed with varicella caused by VZV, and oral administration of valacyclovir was initiated.

However, on the fifth hospital day, she presented with dyspnea and productive cough, and her body temperature was 37.3°C; the Glasgow Coma Scale score was 14 (E4V4M6), her respiratory rate was 30 breaths/min, and her SpO2 was 88% in room air. Chest CT showed multiple nodular shadows and ground-glass shadows (Fig. 1). The CT findings of varicella pneumonia are well described as nodules, nodules with surrounding ground-glass attenuation, patchy ground-glass attenuation, and coalescence of nodules (13, 14); all of which were observed in this case. Laboratory data showed elevated C-reactive protein (11.55 mg/dL) and serum-soluble interleukin-2 receptor (sIL-2R) (2,745 U/mL). At this time, the VZV antigen test using the sample collected from the vesicles was positive. Thus, the blisters were definitively diagnosed as being caused by varicella.

The sputum culture showed methicillin-resistant Staphylococcus aureus (MRSA). However, there was no elevated white blood cell count, and the CT did not exhibit the typical findings of S. aureus-induced pneumonia such as segmental and bronchopneumonic infiltrates. Thus, MRSA was not suspected to be the cause of infection in this case. Based on these findings, her pneumonia was considered to be varicella pneumonia caused by VZV, and intravenous acyclovir administration (750 mg/d) was initiated.

Furthermore, considering the possibility of bacterial pneumonia, ampicillin/sulbactam (3 g intravenously every 8 hours) was administered. MTX and iguratimod were discontinued. However, on the eighth hospital day, her respiratory condition deteriorated, and her chest X-ray findings worsened; thus, endotracheal intubation and mechanical ventilation were started. At this point, a VZV-polymerase chain reaction (PCR) analysis of intratracheally aspirated sputum was positive, and the pneumonia was diagnosed as varicella pneumonia. Therefore, administration of 1,500 mg/day of acyclovir was initiated. Subsequently, both laboratory data and imaging findings steadily improved (Fig. 2).

On the 10th hospital day, the dose of sedative was reduced for extubation, but arousal was not observed. VZV-induced meningitis was suspected, and a cerebrospinal fluid test revealed increased cell counts (81/μL) with lymphocyte

Figure 1. Chest computerized tomography (CT) performed on the fifth hospital day showing multiple nodular shadows and ground-glass shadows.
Figure 2. Clinical course of the case. ACV: acyclovir, ABPC/SBT: ampicillin/sulbactam, CRP: C-reactive protein, CSF: cerebrospinal fluid, FiO2: fraction of inspiratory oxygen, MTX: methotrexate, PCR: polymerase chain reaction, VACV: valacyclovir, VCM: vancomycin, VZV: varicella-zoster virus

predominance, elevated protein levels (179 mg/dL), and mildly decreased glucose levels (59 mg/dL, 160 mg/dL in serum). VZV-PCR was positive, showing VZV meningitis. Therefore, intravenous acyclovir administration was continued for 21 days, according to the European guidelines (15).

On the 19th hospital day, the VZV-IgM titer was 1.53, and the VZV-IgG was >128. Thus, this case was diagnosed as VZV reinfection. Thereafter, the pneumonia and decreased consciousness improved, but left facial nerve palsy and dysphagia remained owing to the sequelae of VZV infection. Magnetic resonance imaging (MRI) on the 57th hospital day showed hyperintensity on the bilateral postero-lateral medulla oblongata and cerebellar peduncle on diffusion-weighted and T2-weighted images, revealing VZV meningoencephalitis (Fig. 3). However, the patient had no new neurological findings. Thus, we decided not to add treatment for encephalitis.

Abdominal contrast-enhanced CT performed on the 43rd hospital day showed that the liver tumor had shrunk (Fig. 4). Furthermore, the blood test on the 4th hospital day revealed EBV infection [EBV viral capsid antigen (EBV-VCA) IgG=1,280, IgM=10, EBV nuclear antigen (EBNA) = 20]. The nucleic acid quantification test of EBV performed using the stored serum sample 10 days before admission showed a high value of 1.3x10^3 copies/mL. In contrast, the EBV nucleic acid quantitative test performed on the 59th day of hospitalization was negative. In addition, sIL-2R levels were normalized. Based on these findings, we were unable to deny the existence of a liver tumor of MTX-associated lymphoproliferative disorder (MTX-LPD). A biopsy could not be performed due to her deteriorating health condition because of the VZV infection.

Discussion

We encountered a rare case of severe pneumonia and meningoencephalitis due to VZV reinfection during immunosuppressive treatment for RA. In addition, this is the first case of VZV reinfection and EBV reactivation.

This is a rare case in which varicella due to VZV reinfection progressed to severe pneumonia and meningoencephalitis in a patient who underwent immunosuppressive treatment. There has been only one previous case of both pneumonia and meningitis due to VZV reinfection, similar to that in our case (9). However, several cases of VZV reinfection have been reported in immunocompromised hosts (2, 16, 17). These previous studies reported cases of pneumonia or lethal septic shock as serious complications (16, 17). Therefore, intravenous high-dose acyclovir is recommended as soon as possible for immunocompromised hosts with varicella (18, 19). In our case, the start of intravenous high-dose acyclovir administration for only varicella might have suppressed the development of severe pneumonia and meningoencephalitis.

Furthermore, we considered that the combination treatment using MTX and iguratimod, as well as old age, con-
Figure 3. Magnetic resonance image performed on the 57th hospital day showing hyperintensity (arrows) at the bilateral posterolateral medulla oblongata and cerebellar peduncle on (a) T2-weighted and (b) diffusion-weighted imaging.

Figure 4. Abdominal computed tomography (CT) with contrast performed (A) at the first visit and (B) on the 43rd hospital day showing shrinkage of the liver tumor (arrows).

tributed to the severity of the VZV infection. MTX is the most commonly used drug for the treatment of RA. A review article revealed that the use of MTX in patients with RA was not associated with the incidence of VZV infection (20). Igruratimod used in our case is a novel synthetic small-molecule disease-modifying anti-rheumatic drug that has shown excellent efficacy and tolerability as an additional treatment when conventional drugs are inadequately effective (21). Previous studies have shown that igruratimod inhibited immunoglobulin production by B cells and suppressed antigen-specific T cell proliferation, suggesting that it had a possible immunosuppressive effect (22, 23). Furthermore, another study showed that patient characteristics, such as old age, chronic pulmonary disease, advanced disease, use of tumor necrosis factor-α inhibitor, and MTX dosages >8.0 mg/week were all significant risk factors for severe infection in patients with RA (24). In the present case, although the only factor of note was the elderly age of the patient among risk factors for serious infection, combination use of MTX and igruratimod is considered a cause of VZV infection. In such cases, sufficient infection control against VZV is ideally required. Therefore, the administration of the herpes zoster subunit vaccine, which reduces the risk of herpes zoster among adults ≥70 years old, should be considered for patients with risk factors being treated with combination immunosuppressive drug therapy for RA (25).

This case was complicated by EBV reactivation and VZV reinfection. There has been only one other case of EBV reactivation and VZV infection, similar to that in our case. This previous case showed EBV-positive LPD, cytomegalovirus reactivation, and VZV encephalitis that developed during treatment for medulloblastoma (26). However, a previous study reported that 33.8% of 161 patients with EBV-related infectious mononucleosis were positive for VZV-specific IgA, whereas healthy controls were negative (p<0.001) (27). Based on these descriptions, when VZV infec-
tion or EBV reactivation is observed, the occurrence of other viral infections should be noted.

We diagnosed the patient with VZV encephalitis because MRI showed hyperintensity at the posterolateral medulla oblongata and cerebellar peduncle on diffusion-weighted and T2-weighted imaging. However, these findings are not typical for VZV encephalitis, as a previous report described vascular lesions as the characteristic feature of VZV encephalitis (28). In contrast, three VZV encephalitis cases with non-vascular lesions, such as brainstem lesions, suggesting rhombencephalitis, have also been reported (29). Therefore, our diagnosis of VZV brainstem encephalitis was considered reasonable.

**Conclusion**

We encountered a rare case of severe pneumonia and meningoencephalitis caused by VZV reinfection, and EBV reactivation during the treatment of RA. Therefore, the occurrence of severe VZV infections and EBV reactivation during the treatment of RA should be noted.

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

**References**

1. Cohen JI. Clinical practice: herpes zoster. N Engl J Med 369: 255-263, 2013.
2. Gershon AA, Steinberg SP, Gelb L. Clinical reinnfection with varicella-zoster virus. J Infect Dis 149: 137-142, 1984.
3. Marin M, Watson TL, Chaves SS, et al. Varicella among adults: data from an active surveillance project, 1995-2005. J Infect Dis 197: S94-S100, 2008.
4. Arvin AM. Varicella-zoster virus. Clin Microbiol Rev 9: 361-381, 1996.
5. Amlie-Lefond C, Kleinschmidt-DeMasters BK, Mahalingam R, Davis LE, Gilden DH. The vasculopathy of varicella-zoster virus encephalitis. Ann Neurrol 37: 784-790, 1995.
6. Chung FR, Lee CH, Chung CH, et al. Varicella-zoster infection with encephalopathy, pneumonia, and renal failure: a case report. Ren Fail 29: 359-362, 2007.
7. Beby-Defaux A, Brabant S, Chatellier D, et al. Disseminated varicella with multiorgan failure in an immunocompetent adult. J Med Virol 81: 747-749, 2009.
8. Teranishi H, Sakiyama M, Nagatoshi Y, et al. Acute lymphoblastic leukemia complicated with varicella zoster virus meningoencephalitis and visceral dissemination after related bone marrow transplantation. Rinsho Ketsueki (Jpn J Clin Hematol) 52: 287-292, 2011 (in Japanese).
9. Yamashita H, Ueda Y, Takahashi Y, Akio M. A case of adult-onset varicella pneumonia and varicella-zoster virus (VZV) meningitis resulting from a reoccurrence of varicella. Kansenshogaku Zasshi (J Jpn Assoc Infect Dis) 86: 306-309, 2012 (in Japanese).
10. Low LL, Vasanwala FF, Suhail SM. Varicella encephalitis and pneumonia in a patient with end stage renal failure. Asia Pac Fam Med 13: 4, 2014.
11. Helou E, Grant M, Landry M, Wu X, Morrow JS, Malinis MF. Fatal case of cutaneous-sparing orolaryngeal zoster in a renal transplant recipient. Transpl Infect Dis 19: e12704, 2017.
12. Takahashi Y, Haru S, Hoseiba R, et al. Pneumonia and central nervous system infection caused by reactivation of varicella-zoster virus in a living-donor kidney transplantation patient: case report and review of the literature. CEN Case Rep 10: 370-377, 2021.
13. Kim JS, Ryu CW, Lee SI, Sung DW, Park CK. High-resolution CT findings of varicella-zoster pneumonia. AJR Am J Roentgenol 172: 113-116, 1999.
14. Frangides CY. Pneumatoïs I. Varicella-zoster virus pneumonia in adults: report of 14 cases and review of the literature. Eur J Intern Med 15: 364-370, 2004.
15. Steiner I, Budka H, Chaudhuri A, et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol 17: 999-1057, 2010.
16. Aihara S, Nakagawa K, Ikemata Y, et al. Varicella reactivation with unilateral varicella pneumonia. Intern Med 55: 3143-3145, 2016.
17. Lehungue S, Rambaud R, Guervilly C, et al. Fatal septic shock triggered by donor transmitted varicella zoster virus infection 3 days after lung transplantation. Transplantation 101: e351-e352, 2017.
18. Tunbridge AJ, Breuer J, Jeffery KJ; British Infection Society. Chickenpox in adults - clinical management. J Infect 57: 95-102, 2008.
19. Gnann JW. Antiviral therapy of varicella-zoster virus infections. In: Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Arvin A, Compadelli-Fiume G, Mocarski E, et al., Eds. Cambridge University Press, Cambridge, 2007.
20. Zhang N, Wilkinson S, Riaz M, Östör AJ, Nisar MK. Does methotrexate increase the risk of varicella or herpes zoster infection in patients with rheumatoid arthritis? A systematic literature review. Clin Exp Rheumatol 30: 962-971, 2012.
21. Xie S, Li S, Tian J, Li F. Igaritamoid as a new drug for rheuma-toid arthritis: current landscape. Front Pharmacol 11: 73, 2020.
22. Aikawa Y, Tanaka N, Shin T, Makino S, Tanaka K, Matsumoto Y. A new anti-rheumatic drug, T614, effectively suppresses the development of autoimmune encephalomyelitis. J Neuroimmunol 89: 35-42, 1998.
23. Tanaka K, Yamamoto T, Aikawa Y, et al. Inhibitory effects of an anti-rheumatic agent T614 on immunoglobulin production by cultured B cells and rheumatoid synovial tissues engrafted into SCID mice. Rheumatology (Oxford) 42: 1365-1371, 2003.
24. Komano Y, Tanaka M, Nanki T, et al. Incidence and risk factors for serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. J Rheumatol 38: 1258-1264, 2011.
25. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N Engl J Med 375: 1019-1032, 2016.
26. Ohts M, Taga T, Nomura A, et al. Epstein-Barr virus-related lymphoproliferative disorder, cytomegalovirus reactivation, and varicella zoster virus encephalitis during treatment of medulloblastoma. J Med Virol 83: 1582-1584, 2011.
27. Karner W, Bauer G. Activation of a varicella-zoster virus-specific IgA response during acute Epstein-Barr virus infection. J Med Virol 44: 258-262, 1994.
28. Bertrand A, Leclercq D, Martinez-Almoyna L, Girard N, Stahl JP, De-Broucker T. MR imaging of adult acute infectious encephalitis. Med Mal Infect 47: 195-205, 2017.
29. De Broucker T, Mailles A, Chabrier S, Morand P, Stahl JP; Steering Committee and Investigators Group. Acute varicella zoster encephalitis without evidence of primary vasculopathy in a caseseries of 20 patients. Clin Microbiol Infect 18: 808-819, 2012.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/ by-nc-nd/4.0/).