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Inflammatory granuloma of the trachea: a rare case with Epstin-Barr virus infection

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Epstein-Barr virus (EBV), a double-stranded DNA virus with an envelope, is a ubiquitous pathogen that is prevalent in humans, although most people who contract it do not develop symptoms (Kerr, 2019). While the primary cells EBV attacks are epithelial cells and B lymphocytes, its target range expands to a variety of cell types in immunodeficient hosts. Serological change occurs in 90% of infected patients. Therefore, immunoglobulin M (IgM) and IgG, serologically reactive to viral capsid antigens, are reliable biomarkers for the detection of acute and chronic EBV infections (Cohen, 2000). Symptoms of EBV infection vary according to age and immune status. Young patients with primary infection may present with infectious mononucleosis; there is a typical triad of symptoms including fever, angina, and lymphadenectasis (Houen and Trier, 2021). In immunocompromised patients, response after EBV infection may be atypical, with unexplained fever. The nucleic acid of EBV can be detected to confirm whether high-risk patients are infected (Smets et al., 2000). EBV is also associated with the occurrence of certain tumors (such as lymphoma and nasopharyngeal carcinoma) because it transforms host cells (Shannon-Lowe et al., 2017; Tsao et al., 2017).

Several relatively rare EBV complications have already been reported. For example, granuloma developed after EBV infection has been found in many types of tissue. Lymphomatoid granulomatosis (LYG), an EBV-driven B-cell lymphoproliferative disease, universally involves the lungs and other extranodal sites, such as the skin, nervous system, liver, and kidneys (Melani et al., 2020). Studies have suggested that EBV infection is associated with the formation of periapical granulomas. Makino et al. (2015) found EBV-encoded small RNA in the cytoplasm and nuclei of B cells and plasma cells in periapical granulomas. Another study that involved polymerase chain reaction (PCR) of EBV from bone-marrow aspiration showed positive results in a patient with multiple fibrin-ring granulomas (Chung et al., 2010). EBV-driven B-cell neoplasms may present as extrinsic gastrointestinal masses (Volaric et al., 2021). The rarity of the virus means that it is easily overlooked in pathological examination. In addition, granuloma formation in the respiratory tract following EBV infection is not well documented. Here, we report the rare case of a patient who almost died from a granuloma in the respiratory tract due to an EBV infection.

A 61-year-old woman was rushed to our emergency department with chest distress and dyspnoea, which had both begun 7 d earlier (Fig. 1). She had suffered sudden cardiac arrest and respiratory failure 5 d previously. The local hospital urgently treated her with cardiopulmonary resuscitation and tracheal intubation. Four days after intubation, the patient was extubated. Since her symptoms had not improved, she was sent to our hospital for further treatment 1 d after extubation. Upon admission, the symptoms of chest distress and dyspnoea had progressively worsened, and the patient had a dry cough and less sputum. She denied fever, chest pain, nausea, or vomiting. Her physical examination revealed the following: jugular vein

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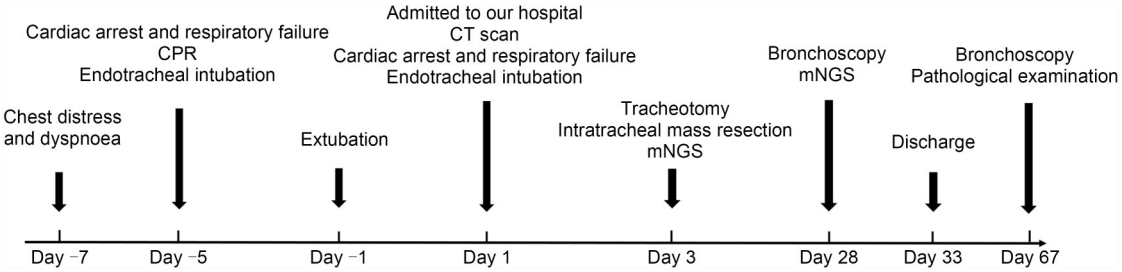

Fig. 1 Timeline of major clinical events of the patient infected with Epstein-Barr virus. CPR: cardiac pulmonary resuscitation; CT: computed tomography; mNGS: metagenomic next-generation sequencing.

distension, coarse breathing sounds in both lungs, wet rales in the right lower lung, completely irregular heart rhythm, and a heart murmur. There was no palpable hepatosplenomegaly or lymphadenopathy. Her blood test indices showed a leucocyte concentration of 17×10^{9} L^{-1} (with 90.7% neutrophils, 3.2% lymphocytes, 6.0% monocytes), a pH value of 7.20, a partial pressure of carbon dioxide of 61.2 mmHg (1 mmHg=0.133 kPa), a partial pressure of oxygen of 94.7 mmHg, hypersensitive C-reactive protein level of 22.9 mg/L, and procalcitonin level of 3.27 ng/mL. It is worth noting that the laboratory test revealed EBV infection with 1.5 signal-to-cutoff ratio (S/CO) immunoglobulin M (IgM) antibody (+) of EBV, 9.9 S/CO IgG antibody (+), and 1.77×10^{3} EBV-DNAs.

We performed a computed tomography (CT) airway-reconstruction scan (Fig. 2a) and then re-intubated the patient due to sudden cardiac arrest and respiratory failure. The CT scan results suggested the presence of a sputum thrombus in the tracheal cavity. A multidisciplinary team (MDT) discussion was then organized, including emergency physicians, otolaryngologists, pulmonologists, radiologists, and clinical nurse specialists, to determine the next step in treatment. It was agreed that rapid removal of the intratracheal mass was essential. Because the intratracheal mass was large and was located below the tracheal tube, bronchoscopic examination or therapy was difficult to carry out. To prevent the mass from blocking the airway and causing asphyxia after extubation, all experts suggested a tracheotomy and intratracheal mass resection as the optimal approach. We carried out the treatment regimen the next day. A necrotic pseudomembranous object was seen in the trachea during the operation and a strip mass about 5 cm in length was removed; these are shown in the video S1 and in Fig. 2b. We also performed metagenomic next-generation sequencing (mNGS) on the tissue samples and detected

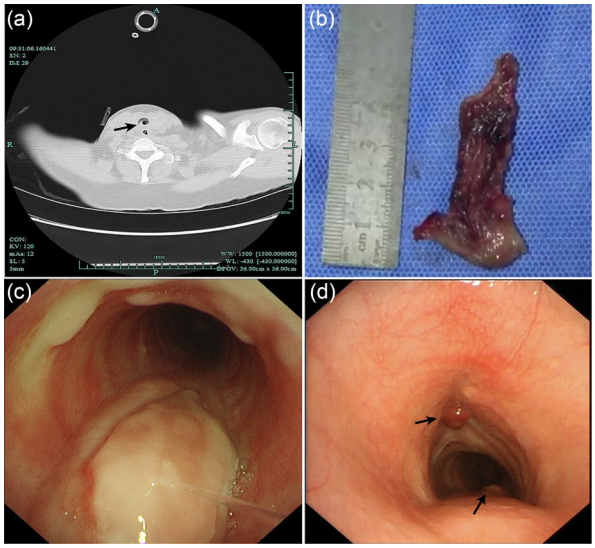

Fig. 2 Imaging, gross morphology, and bronchoscopic data of the patient's mass. (a) The computed tomography (CT) scan image used to reconstruct the airway. Small circular patches of high density were seen in the tracheal lumen (arrow). (b) A 5-cm intratracheal strip mass was removed by intratracheal mass resection. (c) The results of bronchoscopy on postoperative Day 25 (3× magnification). The mucosa of the upper trachea was mildly swollen. (d) The results of follow-up bronchoscopy one month later (3× magnification). Nodular mucosal ridges in the tracheal wall were below the glottis (arrows).

EBV. Postoperative pathology revealed necrotic tissue with neutrophil infiltration. Due to a surgical-site infection, the patient exhibited recurrent fever after the operation, so antibiotics and antiviral drugs were used to control the infection.

On postoperative Day 25, the patient was examined by bronchoscopy (Fig. 2c). The results indicated that the mucosa of the upper trachea was tumefied, and the mucosae of the left and right bronchus were mildly swollen. We took tissue samples for pathogen detection by mNGS; EBV was still detectable in the samples. EBV, which belongs to human gammaherpesvirus 4,

usually spreads through the saliva of an asymptomatic person. Patients may present with atypical clinical manifestations, such as infection, unexplained fever, or other less common complications. Therefore, we hypothesized that the rare neoplasm blocking the respiratory tract was a plasma-cell granuloma resulting from EBV infection.

On postoperative Day 30, the patient was discharged with a tracheostomy tube, and her vital signs were stable. At her last visit for a one-month follow-up, reevaluation by bronchoscopy revealed multiple nodular mucosal ridges in the tracheal wall below the glottis (Fig. 2d). Histopathological examination of the site showed inflammatory granulation tissue with histiocytic aggregation (Fig. 3). These results could indicate that after the EBV infection, the granuloma was tending to relapse, and that more rigorous follow-up was needed.

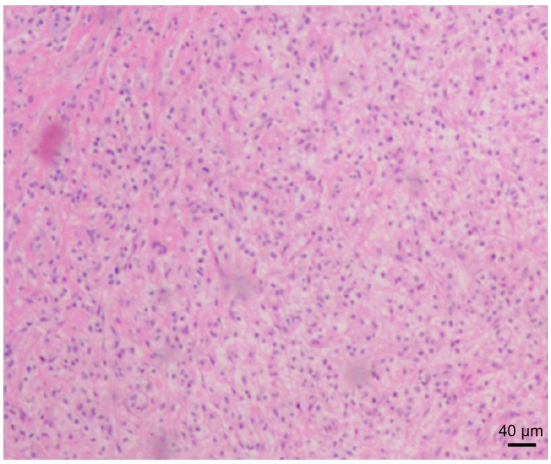

Fig. 3 Histopathological examination results of inflammatory granulation tissue with histiocytic aggregation.

After reviewing this case, we suspect that the patient had an EBV-infected inflammatory granuloma in her respiratory tract. EBV infection can often cause systemic inflammation, such as infectious mononucleosis. EBV granulomas in bone marrow are thought to be associated with infectious mononucleosis (Fiala et al., 1987). However, in this case, the patient did not develop the typical symptoms of infectious mononucleosis. The granulomatous tissue was more likely caused by chronic EBV infection, which is quite common in other tissues (Chung et al., 2010).

In addition to being involved in the pathogenesis of some malignant systemic diseases, EBV has also been shown to be associated with the secretion of inflammatory cytokines. Houen and Trier (2021) found evidence of a correlation between EBV infection and rheumatoid arthritis or Sjögren syndrome. Other studies suggested that EBV may induce immune dysregulation by encoding deoxyuridine triphosphate nucleotidohydrolase (dUTPase); dUTPase inhibits the replication of stimulated peripheral blood mononuclear cells (Glaser et al., 2006; Jiang et al., 2022). EBV also upregulates pro-inflammatory factors such as interleukin (IL)-6, tumor necrosis factor-α (TNF-α), IL-8, and IL-10 (Nakai et al., 2012; Sin and Dittmer, 2012). Of these factors, IL-10 can inhibit the production of IL-2 and interferon-γ (INF-γ) by means of type 1 T helper cells (Th1) (Fiorentino et al., 1991; Lu et al., 2022). When the inflammatory factors secreted by Th1, which control viral infection, are suppressed and those secreted by Th2 take over, local inflammation may occur (Zhang et al., 2021). Thus, EBV may play a role in local inflammation in addition to systemic inflammation. EBV is most commonly transmitted through the respiratory tract, thereby invading the reticuloendothelial cells of the upper respiratory tract (Nowalk and Green, 2016). This may explain why EBV can produce inflammatory granulomas in the respiratory tract. This is also evidenced by mNGS detection of EBV in the patient's airway tissue. Also, in this case, the inflammatory granuloma following EBV infection tended to recur. Further rigorous follow-up was required.

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Author contributions

Zhaodi WANG performed the research and wrote the manuscript. Xuan LU and Yunmei YANG edited the manuscript. Yuanqiang LU contributed to the study design and editing of the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Zhaodi WANG, Xuan LU, Yunmei YANG, and Yuanqiang LU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was

obtained from all patients for being included in the study. This study protocol was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (Study ID: 20230163).

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Supplementary information

Video S1