Transbronchial Lung Cryobiopsy for Diagnosis of Cytomegalovirus Pneumonia in an Immunocompromised Patient: A Case Report

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Cytomegalovirus (CMV) pneumonia is a common infectious disease in immunocompromised patients. Accurate diagnosis of CMV infection is important to improve the survival rate. We reported a middle-aged man with Henoch-Schonlein purpura under long-term immunosuppressant treatment who had fever and dry cough for 1 week. Chest computed tomography showed multiple peribronchial patches and ground glass opacities in bilateral lungs. Community-acquired pneumonia was considered initially and antibiotics were prescribed, but the chest image and clinical symptoms showed progression. Transbronchial lung cryobiopsy (TBLC) was arranged and CMV pneumonia was confirmed by pathology. There was no adverse event after TBLC and the patient recovered well after anti-viral treatment. To our knowledge, this is the first report on the use of TBLC for diagnosis of CMV pneumonia. ***(Thorac Med 2021; 36: 41-46)***

Key words: cytomegalovirus (CMV) pneumonia, endobronchial ultrasound (EBUS), transbronchial lung cryobiopsy (TBLC), virtual bronchoscopic navigation (VBN)

Introduction

Cytomegalovirus (CMV) infection is common in patients with immunocompromised conditions such as hematologic malignancy, post-hematopoietic stem-cell transplantation, post-solid organ transplantation, human immunodeficiency virus infection, and autoimmune disease, and in those receiving immunomodulating medications [1-3]. Although image pattern, serology study or microbiologic study of a respiratory specimen can be used for diagnosis of CMV pneumonia, surgical lung biopsy remains the gold standard for accurate diagnosis [1, 4-6]. However, surgical lung biopsy cannot be safely performed when patients have respiratory distress and co-morbidities [7, 8]. An alternative diagnostic method with a lower complication rate is needed. Here, we report the first case of a CMV pneumonia patient diagnosed by

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transbronchial lung cryobiopsy (TBLC).

Case Report

A 60-year-old man presented to our hospital with fever for 1 week, accompanied with dry cough and watery diarrhea. There was no associated hemoptysis, chest tightness, abdominal pain, myalgia, arthralgia, or skin eruptions. He had a medical history of Henoch-Schonlein purpura under daily prednisolone 20 mg and mycophenolate mofetil 1000 mg support. On initial physical examination, the patient was ill-looking with a respiratory rate of 20/min, blood pressure of 121/68 mmHg, heart rate of 118/min and body temperature of 36.6 degrees Celsius. Chest auscultation disclosed bilateral coarse breathing sounds. Other examinations, including the cardiovascular, abdominal, central nervous and musculoskeletal system, were unremarkable. Laboratory results showed a normal hemogram, biochemistry, and electrolyte level, except mild anemia with hemoglobin 9.0 g/dL. Initial chest radiograph (CXR) showed ill-defined opacities in bilateral lung fields, especially the upper lung (Figure 1A). Chest computed tomography (CT) disclosed multiple peribronchial patches and ground glass opacities in bilateral lungs. There were also some subpleural opacities and pleural effusion bilaterally (Figure 1B). Bacterial pneumonia or Pneumocystis jiroveci pneumonia was suspected initially; therefore, empiric antibiotics with cefepime and trimethoprim/sulfamethoxazole were administered. However, serial CXR showed progression of the lung parenchymal lesions. Microbiologic studies including bacteria, mycobacteria and fungus yielded negative results and the autoimmune profile revealed no abnormal finding. Histologic proof was suggested as necessary for the final diagnosis and treatment. The patient declined surgical biopsy, and we therefore suggested bronchoscopic biopsy.

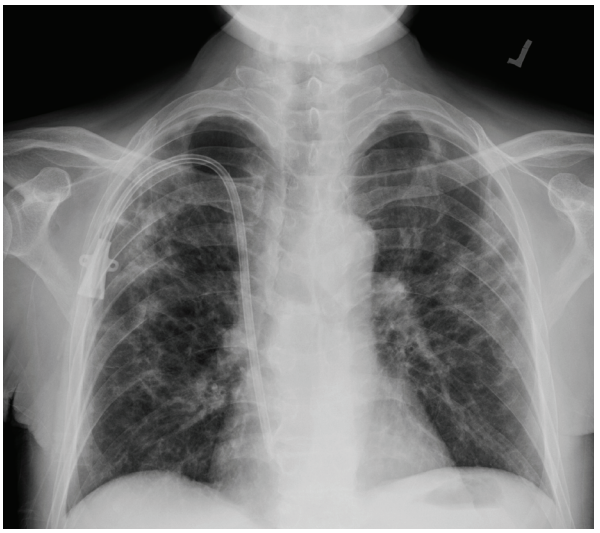

Fig. 1A. Initial chest radiograph revealed bilateral diffuse reticular lesions combined with some consolidations.

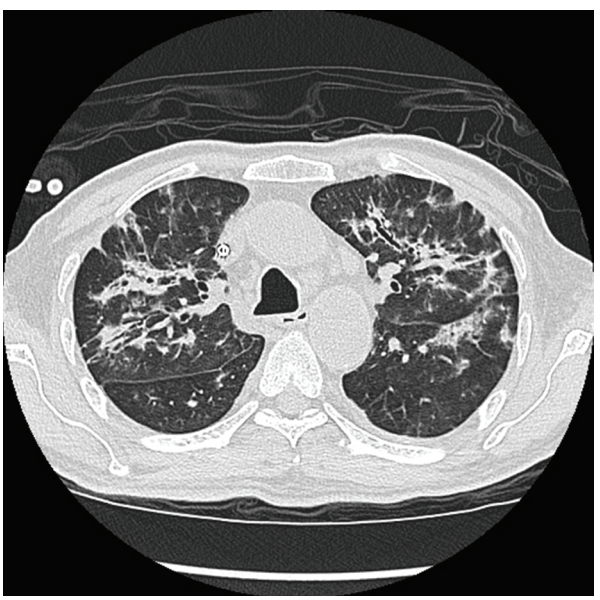

Fig. 1B. Chest computed tomography revealed multiple peribronchial and subpleural patches and peribronchial ground glass opacities in bilateral lungs.

Flexible bronchoscopy (BF-IT260; Olympus Co., Tokyo, Japan) was then performed in a bronchoscopy room setting. After premedication with lidocaine as a local anesthesia, and

with intravenous midazolam and fentanyl for conscious sedation, the scope was inserted through the oral route. We used a commercial navigation planning system (LungPoint® Planner; Broncus Technologies, CA, USA) to select the target lesion and the target bronchus (Figure 2A). The 20 MHz radial endobronchial ultrasound (EBUS) (UM-S20-17S; Olympus Co., Tokyo, Japan) probe was inserted through the working channel of the scope into the target bronchus. A peribronchial lesion with homogenous echogenicity was detected surrounding the right third bronchus under EBUS study (Figure 2B). A 1.9-mm cryoprobe (ERBOKRYO CA, ERBE, Tuebingen, Germany) was then inserted through the working channel of the scope into the target bronchus for TBLC, and carbon dioxide was used as a cooling system. Once brought into position, the probe was cooled for approximately 5–6 seconds, and then was retracted with the frozen lung tissue attached to the probe's tip. The frozen specimen was thawed in saline and then transferred to formalin for fixation. No severe complication was noted after the procedure, except self-limited wound oozing.

The pathologic report revealed scattered cells with large intranuclear inclusion and some intracytoplasmic inclusion in the alveolar lining cells, which were highlighted by CMV immunostaining (Figure 3). The diagnosis of CMV pneumonia was made and the patient was given ganciclovir for 3 weeks without complications. CXR follow-up revealed the bilateral lung opacities were in resolution.

Fig. 2A. The target lesion and target bronchus were localized using a commercialized planning system before the procedure.

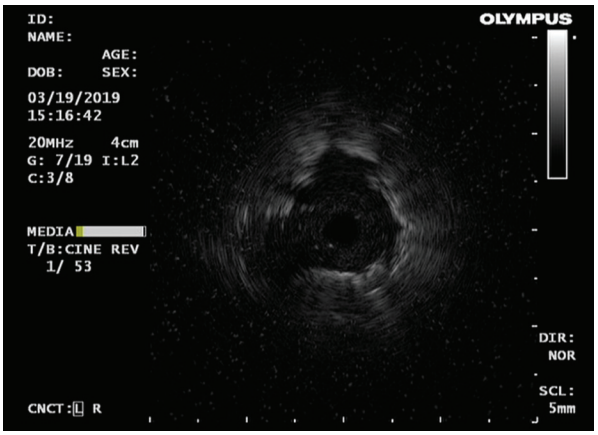

Fig. 2B. Concentric hypoechoic lesions noted under radial EBUS probe at the right 3rd segment.

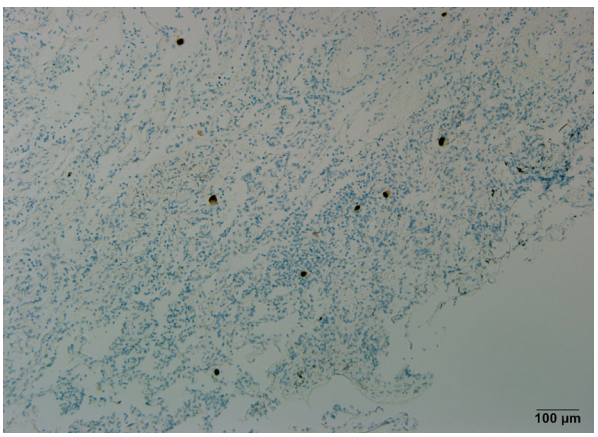

Fig. 3. Inclusion bodies under CMV immunostaining.

Discussion

Accurate diagnosis of CMV pneumonia is important for treatment. The presentation of

clinical symptoms and signs, such as hypoxia, tachypnea, dyspnea or new infiltrates on imaging is generally nonspecific. The CXR or CT imaging pattern is similar to that of connective tissue disease-associated interstitial lung disease or other atypical infections. CMV can be detected from respiratory specimens obtained by expectoration, bronchial washing, or bronchoalveolar lavage (BAL). However, a CMV viral culture is not clinically useful because it takes 2 to 3 weeks to obtain the result [9]. Polymerase chain reaction for CMV (CMV-PCR) is a molecular technique used for identification of the CMV viral load. Some studies reported that CMV-PCR had a sensitivity of more than 90% and specificity of 70~77% in BAL fluid [5, 10-13]. Nevertheless, there is no consensus on the threshold of the CMV DNA (deoxyribonucleic acid) viral load in BAL fluid for use in the diagnosis of CMV pneumonia. There was also a high prevalence of asymptomatic viral shedding [1]. Pathologic diagnosis via lung biopsy is more crucial for this type of patient.

Transbronchial lung biopsy (TBLB) is the conventional method of obtaining a specimen from the lung parenchyma with biopsy forceps. However, the diagnostic accuracy of TBLB was only 29~53% because of the small specimens [7, 14]. In this case, cryobiopsy was used to obtain a better diagnostic yield. Compared to forceps biopsy, cryobiopsy had larger tissue samples (11-15 mm2), less crush artifact and higher diagnostic accuracy (75-80%) for interstitial lung disease [8, 14-16]. The size of the tissue specimen from our patient was 18-21 mm2, and typical histological findings of CMV infection (intranuclear and intracytoplasmic inclusion under CMV immunostaining) were easily obtained. Though there is no report on the use of cryobiopsy for diagnosing CMV pneumonitis, we believe that TBLC could be an alternative choice in this situation.

The most common complications of TBLC are pneumothorax (2-11%) and bleeding (2-25%) [17]. TBLC under fluoroscopy was suggested to avoid pleural injury, and rigid bronchoscopy with an endobronchial blocker has been used to minimize bleeding [14, 18, 19]. However, the tools needed for these 2 procedures are unavailable in most bronchoscopy units in Taiwan. To lower the complication rate in our patient, we incorporated virtual bronchoscopic navigation (VBN) and EBUS for the TBLC procedure. In Ishida`s study, there was high agreement between virtual bronchoscopic images and actual bronchi, enabling the bronchoscope to be inserted more accurately and more peripherally [20]. We used VBN to choose the proper site for biopsy, which was neither too close to the pleura nor accompanied by too many vessels. We also used EBUS for evaluating the detailed information of the target lesion during the procedure. EBUS could also help us avoid the hypervascular area, thereby decreasing the bleeding risk [20-22]. The patient experienced no adverse event (bleeding or pneumothorax) when combining VBN and EBUS during the procedure.

Some experts have advocated surgical lung biopsy for the diagnosis of diffuse lung lesions. The diagnostic yield of TBLC is slightly lower than that of video-assisted thoracoscopic surgery (VATS) lung biopsy (82.8% vs 98.7%) because the median sample size of surgical lung biopsy is larger (46.1±13.8 mm) [17, 23]. Nevertheless, patients that underwent TLBC had a shorter duration of hospitalization (2.6 days vs 6.1 days, $p<0.001$) and lower mortality due to adverse events (2.7% vs 0.3%, $p=0.045$) [17]. TBLC had lower complication and moral-

ity rates, and was also more cost-effective than VATS lung biopsy [8, 15]. VATS lung biopsy could be reserved for patients when a diagnosis is not reached with TBLC.

There is a disadvantage to using TBLC for diagnosis of infectious disease, since frozen samples are not suitable for microbiological studies. The microorganism may not be alive and a frozen section is difficult to culture. In Sanchez-Cabral`s report, more microorganisms could be cultured on BAL samples than on TBLC samples [24]. However, we did not perform BAL for microbiologic culture in this patient. The patient had no fever and no toxic signs at that time, and interstitial lung disease was considered the first priority after multidisciplinary discussion. Without BAL, a misdiagnosis could occur in patients with an infectious disease. The combination of TBLC and BAL might give us more information, helping us to make an accurate diagnosis.

To our knowledge, this is the first case report of CMV pneumonia diagnosed by TBLC. TBLC provides a less invasive, more cost-effective and more definite diagnosis in patients with diffuse lung lesions. It is an alternative choice for patients who decline surgery or who are at high risk with surgical biopsy.

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