□ CASE REPORT □

Esophagomediastinal Fistula Secondary to Multidrug-resistant Tuberculous Mediastinal Lymphadenitis

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Abstract

Esophagomediastinal fistula secondary to mediastinal tuberculosis (TB) lymphadenitis is a rare and unusual complication. A 32-year-old woman visited our clinic because of chest pain. Computed tomography (CT) demonstrated an esophagomediastinal fistula with subcarinal lymphadenopathy and no remarkable parenchymal lung lesions. The esophagomediastinal fistula was confirmed by esophagoscopy; however, the patient's bronchoscopy findings were unremarkable. The endobronchial ultrasound-guided lymph node aspiration did not confirm a diagnosis of TB. Finally, the patient was diagnosed via a lymph node biopsy. A drug-sensitivity test revealed the presence of a multidrug-resistant pathogen. To the best of our knowledge, this is the first case of esophagomediastinal fistula secondary to multidrug-resistant (MDR-) TB mediastinal lymphadenitis.

Key words: mediastinal tuberculous lymphadenitis, esophagomediastinal fistula, multidrug-resistant tuberculosis

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Introduction

Mediastinal tuberculosis (TB) lymphadenitis is a rare clinical manifestation of tuberculosis in adults (1-3). Furthermore, esophagomediastinal fistula formation secondary to mediastinal TB lymphadenitis is an unusual complication that occurs as a consequence of erosion of the adjacent organs (4-6). Herein we describe a case of esophagomediastinal fistula secondary to multidrug-resistant (MDR-) mediastinal TB lymphadenitis.

Case Report

A 32-year-old woman was referred to our hospital because of chest pain and a nodule observed on a chest X-ray. Two months prior to her visit, she had experienced fever

and night sweats. She had undergone a right ovariectomy 14 years prior to this manifestation for ovarian cancer. She was a nonsmoker with no other relevant medical history and denied using illicit drugs. On examination, she appeared well. Her body weight was 48 kg, her height was 160 cm, her temperature was 36.2°C, her blood pressure was 120/70 mmHg, her pulse was 75 beats/min, her respiration rate was 20/min, and her oxygen saturation was 94 to 96% while breathing ambient air. Her laboratory data, including whole-blood interferon gamma release assay (IGRA) results using the QuantiFERON-TB Gold In-Tube test (Cellestis, Carnegie, Australia) and a serological test for the human immunodeficiency virus antibody, were negative. We conducted acid-fast bacilli (AFB) stains and cultures with sputum samples three times but, all of the AFB smears and cultures were negative.

A chest radiograph showed an irregularly shaped nodular

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Figure 1. (A) Chest radiograph performed at the time of presentation showed an irregularly shaped nodular opacity in the right upper lung field. (B) Nonenhanced CT revealed show a fibrocalcified nodule in the posterior segment of the right upper lobe without other parenchymal lung lesions.

Figure 2. A contrast-enhanced CT scan showed partially enhancing, necrotic, and irregular lymphadenopathy along the right lower paratracheal (A), subcarinal (B), and right hilar (C) areas. There was an oval or linear gas collection in an enlarged right lower paratracheal and subcarinal lymph node (A and B). There was a communication (arrowhead) between the esophagus and a mediastinal area for air attenuation (D).

opacity in the patient's right upper lung field (Fig. 1A). A computed tomography (CT) scan of the chest revealed a fibrocalcified nodule in the posterior segment of the right upper lobe without parenchymal lung lesions (Fig. 1B), as well as partially enhancing, necrotic, and irregular lymphadenopathy along the right hilar, subcarinal, and paratracheal areas (Fig. 2A-C). Furthermore, it showed an irregular cystic space suggesting a fistulous connection between the esophagus

and the subcarinal lymph node (Fig. 2D). Positron emission tomography(PET)/CT showed high fluorodeoxyglucose uptake in the area that was suggestive of a fistulous connection between the esophagus and the subcarinal lymph node, without remarkable uptake in other mediastinal lymph nodes (Fig. 3). Endoscopy was subsequently performed, and it showed an ulcerated lesion 5 mm in diameter that was located 32 cm from the upper incisor that suggested the exis-

Figure 3. PET/CT of a fused transaxial view showed high fluorodeoxyglucose uptake (arrowhead) in the fistulous connection located between the esophagus and the subcarinal lymph node.

Figure 4. An esophagoscopic view of the esophagomediastinal fistula (arrowhead) at a site located 32 cm from the upper incisor.

Table. Drug Sensitivity Test to Anti-tuberculous Drugs Based on Absolute Concentration Method Using Löwenstein-Jensen Medium

Name of drug	Drug concentration (ug/mL)	Reading of culture†	Result
Isoniazid	0.2	+++	Resistant
Rifampicin	40	+++	Resistant
Rifabutin	20	+++	Resistant
Ethambutol	2.0	+	Resistant
Pyrazinamide	NR*		Sensitive
Amikacin	40	-	Sensitive
Capreomycin	40	-	Sensitive
Kanamycin	30	-	Sensitive
Streptomycin	4.0	+++	Resistant
Moxifloxacin	2.0	-	Sensitive
Levofloxacin	2.0	-	Sensitive
Ofloxacin	2.0	-	Sensitive
Prothionamide	40	-	Sensitive
Cycloserine	40	-	Sensitive
Paraaminosalicylic acid	1.0	-	Sensitive

*Not recommended

†+, <100 isolated colonies; ++, 101-200, isolated colonies;

+++, 201-500 isolated colonies.

tence of an esophagomediastinal fistula (Fig. 4).

She underwent bronchoscopy via endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). The specimen of subcarinal lymph node exhibited only necrosis with several lymphocytes and neutrophils, and it was negative for AFB staining and TB polymerase chain reaction (PCR). Therefore, we decided to perform mediastinoscopy to achieve an accurate diagnosis and to treat her empirically with isoniazid, rifampicin, ethambutol, and pyrazinamide. Ten days later, a mediastinoscopy and biopsies were performed to obtain tissue from the right lower paratracheal and subcarinal lymph nodes. The biopsies of the right lower paratracheal and subcarinal lymph nodes showed only necrotic tissue and inflamed granulation tissue, respectively. These biopsy samples were also negative for AFB staining and TB PCR. A tissue culture of the subcarinal lymph node performed four weeks later was positive for *Mycobacterium tuberculosis*, whereas the right lower paratracheal lymph node was negative for this pathogen.

At the time of the tissue culture report, she had been receiving anti-TB medication for five weeks, but her clinical status had not improved. We then performed a reverse hybridization-based line probe assay (LPA) and a solid-media drug-sensitivity test (DST). Six days later, the LPA revealed that the pathogen had mutations in the *katG* and *rpoB* genes; therefore, she was suspected of having mediastinal TB caused by an MDR pathogen. The antituberculous treatment was changed to ethambutol, pyrazinamide, kanamycin, moxifloxacin, prothionamide, and cycloserine. A solid-media DST performed at the Korean Institute of TB using the proportion method yielded results that were consistent with MDR-TB four weeks after the initial isolation of *M. tuberculosis*. It showed that the pathogen was resistant to ethambutol and streptomycin, in addition to isoniazid and rifampicin (Table).

Finally, the patient was diagnosed with an esophagomediastinal fistula secondary to MDR-TB mediastinal lymphadenitis. Her antituberculous therapy has been maintained using the above-described regimen, except ethambutol was omitted. Two months after beginning treatment for mediastinal TB, her clinical status had improved. After three months of antituberculous therapy, chest contrast CT showed mediastinal lymphadenopathy improvement with no visible cystic space suggesting a fistulous connection (Fig. 5).

Discussion

Mediastinal TB lymphadenitis without parenchymal lung lesion is an unusual manifestation of TB; however, it occurs more commonly in Asians and black adults (2).

In contrast with pulmonary TB, the conventional methods used to diagnose mediastinal TB lymphadenitis without endobronchial or parenchymal lung lesions, such as respiratory specimen studies using sputum or bronchoscopy, are not effective (7). Although it has been reported that bronchoscopy has a role in the diagnosis of intrathoracic TB lymphadenitis, the majority of the patients included in those studies had endobronchial TB or concomitant parenchymal le-

Figure 5. Contrast-enhanced CT scan after three months of treatment showed improvement of the mediastinal lymphadenopathy along the right lower paratracheal (A), subcarinal (B to D), and right hilar (B) lymph nodes with no visible cystic space suggestive of a fistulous connection.

sions (8, 9). Therefore, the diagnosis of mediastinal TB lymphadenitis without endobronchial or parenchymal lung lesions remains a serious problem because of the limitations of the diagnostic modalities. Furthermore, clinical experience suggests that imaging changes cannot be found immediately after treatment for TB lymphadenitis, and paradoxical responses may also occur, leading to an uncertain diagnosis (7). Therefore, it is necessary to confirm the correct diagnosis of TB based on pathological and bacteriological evidence.

For the purpose of establishing a definite diagnosis and proper management according to the DST profile, more invasive procedures, such as CT-guided fine-needle aspiration biopsy, mediastinoscopic lymph node biopsy, or EBUS-TBNA, are used instead of conventional methods (2, 7, 10, 11). CT-guided fine-needle aspiration is only possible when the patient has a huge mediastinal lymphadenopathy, allowing the lymph node tissue to be obtained while avoiding the vascular structure of the mediastinum. However, these are rare cases, and the diagnostic yield of CT-guided fine-needle aspiration is no higher than that of EBUS-TBNA or mediastinoscopy (2, 10, 11). Although mediastinoscopy achieves the highest diagnostic yield, it is invasive, expensive, and requires inpatient general anesthesia; moreover, it has the disadvantage of overcoming the inaccessibility of the posterior subcarinal and hilar nodes (10, 11). EBUS-TBNA was recently described as an important tool for the diagnosis of mediastinal lymphadenopathy, including TB lymphadenitis (7, 10).

In our case, the patient was not diagnosed as having me-

diastinal TB lymphadenitis by bronchoscopy or EBUS-TBNA. There was no endobronchial lesion evident on bronchoscopic exam. The tissue obtained by EBUS-TBNA only exhibited necrosis with several lymphocytes and neutrophils. There was no epithelioid granulomatous reaction or caseation, and the patient had negative TB PCR, AFB staining, and culture of the subcarinal lymph node. Two previous studies of EBUS-TBNA reported that the necrosis observed in the pathological examination was associated with a higher yield of positive culture because of a higher bacillary load in the lymph node, which causes necrosis (7, 10). Unfortunately, we could not identify the pathogen through EBUS-TBNA, and the additional diagnostic method of mediastinoscopy was required. When EBUS-TBNA was carried out, we performed TBNA three times and obtained approximately 0.5 mL of tissue. The amount of tissue obtained by TBNA is not small in quantity. We hypothesize that it may be affected by esophagomediastinal fistula formation and sampling in a single station of the subcarinal lymph node (10, 12). The EBUS-TBNA uses a small 22-gauge needle, which raises the potential of obtaining false-negative results, especially in the diagnosis of benign disease (sarcoidosis, tuberculosis, etc.) or lymphoma, as the core tissue is smaller than that obtained from mediastinoscopy. Furthermore, it is more difficult to obtain accurate tissue samples for diagnosing a complicated lymph node, such as esophagomediastinal fistula. In fact, EBUS-TBNA has an inferior negative predictive value compared with mediastinoscopy (13).

Drug-resistant TB is a global concern. However, the over-

all incidence of TB has been reported to be slowly decreasing since 2004 due to the efforts of the World Health Organization (WHO) Stop TB Strategy. Nevertheless, there is no definitive evidence that the incidence of MDR-TB is decreasing, despite this global effort (14). Although considerable efforts in several countries, including South Korea, have led to a slow decrease in the overall incidence of TB, surveillance indicates that the incidence of MDR-TB is rising. In South Korea, MDR-TB strains account for 2.7-3.9% of new TB cases and 14.0-27.2% of previously treated cases (15).

Only two South Korean studies about TB lymphadenitis have been published (16, 17). They reported 373 and 110 cases of TB lymphadenitis, respectively, but only one case was diagnosed as mediastinal TB lymphadenitis with subcarinal lymph node involvement. Although the incidence of the MDR-pathogen in extrapulmonary TB is not well known, physicians should be aware of the possibility of MDR-TB in circumstances in which moderate levels of resistance in the TB patient population are predicted (18, 19).

It is known that a number of risk factors for MDR-TB have been critical in its emergence. Almost all are related to the poorly functioning National Tuberculosis Program. Other important risk factors are associated with the supply or quality of the drugs, the possibility of inadequate drug intake by patients, the influence of the private sector, deficient infection control in health centers and hospitals, and the possible high prevalence of highly virulent MDR-TB strains of *M. tuberculosis*. Many other risk factors for MDR-TB have been also identified: previous TB treatment, irregular treatment, female sex, nonpermanent residents, urban migration, urban residence, frequent travelers, younger age, lack of a sewage system in the home, alcoholism plus smoking, and lung cavities (20). In our case, the patient's risk factors for MDR-TB were female gender, urban residence, and young age.

In South Korea, all *M. tuberculosis* isolates are referred for DST to the Korean Institute of Tuberculosis, a WHO-designated Supranational Reference Laboratory. The solid media DST was performed by the proportion method based on resistance to each drug tested and was defined as $\geq 1\%$ bacterial growth in Löwenstein-Jensen medium containing antituberculosis drugs. Pyrazinamide susceptibility was determined using the pyrazinamidase test (15). However, this technique is relatively time consuming; the median interval from initiation of anti-TB treatment to the receipt of DST results is as long as two to three months (21). In this case, we were able to detect MDR-TB more rapidly using a molecular (genotypic) method than with conventional (phenotypic) methods, such as solid- and liquid-media DST, so we could administer adequate and effective anti-TB treatment without delay. The reverse hybridization-based LPA has been developed for the direct detection of MDR-TB strains in clinical specimens. The GenoType MTBDRplus (Hain Lifescience, Nehren, Germany) assay detects MDR-TB by simultaneously detecting mutations in hot-spot regions of the *rpoB*

gene to indicate rifampicin resistance and mutations in *katG* 315 and *inhA* regulatory regions to indicate isoniazid resistance (22).

In our case, the serum IGRA level yielded a negative result. However, the IGRA studies focused on the detection of active pulmonary TB, but there are limited data of diagnostic performance focused on extrapulmonary TB, such as tuberculous lymphadenitis (23-26). Although there was a very small number of patients (total 68 patients with TB lymphadenitis), the IGRA showed a sensitivity of approximately 90% in TB lymphadenitis based on these studies. It is a relatively higher sensitivity than those of other forms of extrapulmonary TB; this can be explained by the fact that localized TB may be the result of a more efficient immune response, which allows for the detection of Interferon-gamma production, whereas more extensive TB can be consistent with deficient interferon-gamma production, which leads to false-negative IGRA results (24, 27). In our case, the patient had mediastinal lymphadenitis, which was different with patients in previous studies. Most patients of the previously mentioned four studies had superficial cervical lymphadenitis without deep lymph node involvement, such as mediastinal lymphadenitis. We think that deep lymph node involvement is the possible reason for the patient's negative IGRA based on the transmission and natural course of TB. In addition, fistula formation as a result of TB may occur in the setting of uncontrolled localized TB, and it is possibly thought to be a more extensive form of TB.

Almost all cases of esophagomediastinal fistula secondary to TB did not require interventional support, such as esophageal stenting, except one pediatric case (4-6). That patient underwent esophageal stenting because they also had a trachea-esophageal fistula. The present patient was instructed to take food and medication via a nasogastric tube for eight weeks after the diagnosis of an esophagomediastinal fistula secondary to TB. She was able to take food and medication normally three weeks after effective treatment of MDR-TB.

In conclusion, we performed mediastinoscopy to confirm the diagnosis of esophagomediastinal fistula secondary to MDR-TB mediastinal lymphadenitis. Although EBUS-TBNA has been used recently in the rapid diagnosis of mediastinal TB lymphadenitis with an increasing diagnostic yield, its role can be limited in complicated cases, such as patients with esophagomediastinal fistulae. To the best of our knowledge, this is the first description of esophagomediastinal fistula secondary to MDR-TB mediastinal lymphadenitis.

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

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