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Respiratory Diseases

Case 17: A 62-Year-Old Man With Dyspnea and Chest Discomfort for 1 Month

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PRESENTATION OF THE CASE 17

Dr. Jeong Hyeon Seong: A 62-year-old man presented to the outpatient clinic with shortness of breath and chest discomfort.

His shortness of breath had started about a month ago, and it had worsened to New York Heart Association (NYHA) class III in the past two weeks. He also had chronic cough and increased sputum production. Chest X-ray taken at the outpatient clinic showed evidence of right pleural effusion, which prompted admission to proceed effusion drainage and analysis (**Fig. 1A**).

The patient had underlying ischemic cardiomyopathy, diabetes mellitus, chronic kidney disease probably due to diabetes, and diabetic retinopathy. He had quit smoking in 2017 after approximately 40 years of smoking. In 2017, he underwent coronary artery bypass grafting (CABG) at this hospital and had a history of two subsequent percutaneous coronary interventions (PCIs) and percutaneous transluminal angioplasty (PTA) for peripheral arterial occlusive disease (PAOD).

On physical examination, his blood pressure was 102/53, heart rate was 71, respiratory rate was 18, and temperature was 36.5°C. He was receiving supplemental oxygen via nasal prongs at 5L/min, with oxygen saturation of 97%. He appeared acutely ill, and decreased breath sounds were noted on the right lower lung field on auscultation.

His complete blood count showed a mild decrease in hemoglobin level (11.7 g/dL) and eosinophilia (8.7%). The blood chemistry results showed a mild C-reactive protein elevation (1.5 mg/dL), elevated urea nitrogen (61.3 mg/dL), creatinine (2.99 mg/dL), uric acid (11.0 mg/dL), and potassium at (5.7 mmol/L). As for cardiac markers, creatine kinase-MB (CK-MB) level was normal (1.31 ng/mL) but slightly elevated troponin T (0.075 ng/mL) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP; 449.0 pg/mL) were noted. Electrocardiogram showed a regular sinus rhythm with a heart rate of approximately 72 beats per minute. Three consecutive sputum acid-fast bacilli (AFB) smears showed negative results,

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Cho HJ. Data curation: Lee JM, Seong JH, Hong YJ, Seo W. Supervision: Min J. Writing - original draft: Lee JM. Writing - review & editing: Cho HJ.

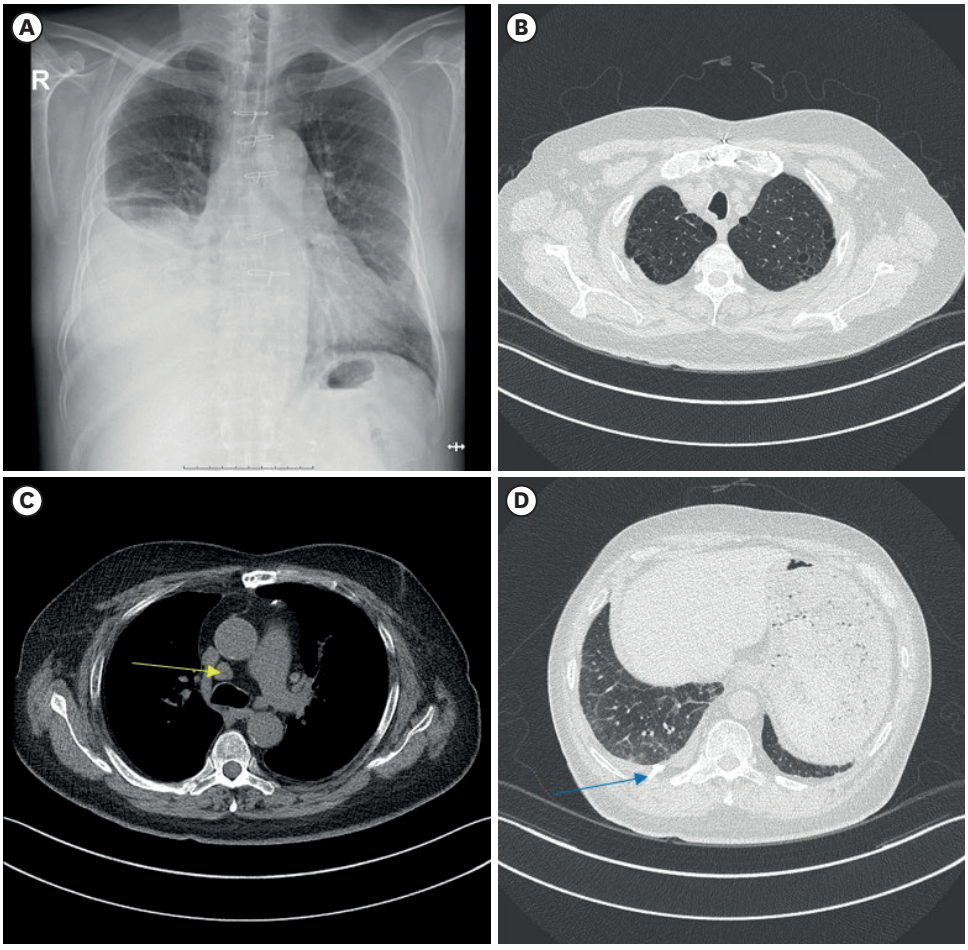

Fig. 1. Chest X-ray and chest computed tomography image. (**A**) Chest X-ray taken at the outpatient department before admission. (**B-D**) Chest computed tomography taken after the right pleural drainage by pleural catheter, showing mild emphysema at both upper lungs (**B**), a few mediastinal lymph node enlargement (arrow) (**C**), subpleural reticular opacities at both lower lungs, small residual pleural effusion, and drainage catheter (arrow) at right lower lung (**D**).

and sputum Xpert MTB/RIF assay, *Mycobacterium tuberculosis* culture and interferon-γ release assay (IGRA) were also negative. Serum total immunoglobulin E (IgE) level was elevated at 1,860.3 IU/mL, but mast allergy test showed no significant finding (**Table 1**).

After performing right pleural pigtail insertion and analyzing the pleural fluid, the results of the analysis were: pH 7.4, white blood cell count 2,260/uL (lymphocytes 51%), red blood cell count 2,300/uL, protein 5.051 g/dL, glucose 90 mg/dL, lactate dehydrogenase 156 U/L, NT-proBNP 480 pg/mL, and adenosine deaminase (ADA) 128.0 IU/L. AFB smear and *M. tuberculosis* polymerase chain reaction (PCR) tested on pleural fluid were negative, and no growth in *M. tuberculosis* culture (**Table 2**). Cytology showed no atypical or malignant cells in the pleural effusion.

CLINICAL IMPRESSION

Dr. Jeong Hyeon Seong: The presence of a unilateral pleural effusion, along with a lympho-dominant exudate and an elevated ADA level of 128.0, strongly suggestive of tuberculous pleuritis.

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Table 1. Initial lab findings of the patient

Parameters	Initial result	Reference range
WBC count, 10^3/L	7.93	4.0–10.0
RBC count, 10^3/L	3.85▼	4.5–5.5
Hemoglobin, g/dL	11.7▼	13.0–18.0
Hematocrit, %	36.8▼	40.0–54.0
Platelet, 10^3/L	240	150–450
WBC differential, %		
Seg. neutrophils	60.1	50–75
Lymphocytes	22.4	20–44
Monocytes	8.3	2–9
Eosinophils	8.7▲	0–5
Basophils	0.5	0–2
ANC, 10^3/L	4.77	
CRP, mg/dL	1.50▲	0–0.5
Glucose, mg/dL	94	50–100
Urea nitrogen, mg/dL	61.3▲	6.0–20.0
Creatinine, mg/dL	2.99▲	0.7–1.2
eGFR, CKD-EPI	21	mL/min/1.73 m^2
Total protein, g/dL	8.2	6.6–8.7
Albumin, g/dL	3.8	3.5–5.2
AST(GOT), U/L	18	0–40
ALT(GPT), U/L	9	0–41
Alkaline phosphatase, U/L	98	40–129
Total bilirubin, mg/dL	0.21	0–1.2
Uric acid, mg/dL	11.0▲	3.4–7.0
LDH, U/L	191	0–250
Sodium, mmol/L	136	136–145
Potassium, mmol/L	5.7▲	3.5–5.1
Chloride, mmol/L	108	98–110
CK-MB, ng/mL	1.31	< 5
Troponin T, ng/mL	0.075▲	< 0.014
NT-proBNP, pg/mL	449.0▲	< 300
(Sputum) AFB smear #1	Negative	Negative
(Sputum) AFB smear #2	Negative	Negative
(Sputum) AFB smear #3	Negative	Negative
(Sputum) MTB X-pert	Negative	Negative
IGRA	Negative	Negative
Total IgE, IU/mL	1,860.3▲	0–158

Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Seoul St. Mary's Hospital are for adults who do not have medical conditions that could affect the results.
WBC = white blood cell, RBC = red blood cell, ANC = absolute neutrophil count, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, CKD-EPI = chronic kidney disease epidemiology collaboration, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GOT = glutamic oxaloacetic transaminase, LDH = lactate dehydrogenase, CK-MB = creatine kinase-MB, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, AFB = acid-fast bacilli, IGRA = interferon-γ release assay, IgE = immunoglobulin E.

IMAGE PRESENTATION

Dr. Jeong Hyeon Seong: After draining the right pleural effusion, a chest computed tomography (CT) scan was performed to evaluate parenchymal lung lesion. Given the patient's underlying chronic renal failure, the CT was performed without contrast enhancement (**Fig. 1B-D**).

The CT findings revealed mild emphysema at both upper lungs and subpleural reticular opacities at both lower lungs, few mediastinal lymph node enlargement, small residual pleural effusion, and drainage catheter at right lower lung. There was no evidence of lung parenchymal lesions suggesting pneumonia or pulmonary tuberculosis (TB).

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Table 2. Pleural effusion fluid analysis

Fluid	Values
Body fluid analysis	
pH	7.4
Color	Yellow
WBC count, cells/uL	2,260
RBC count, cells/uL	2,300
Differential count, %	
Neutrophils	25
Lymphocytes	51
Eosinophils	2
Basophils	1
Macrophage	17
Mesothelial	4
Pleural fluid chemistry	
Protein, g/dL	5.051
Glucose, mg/dL	90
Albumin, g/dL	2.39
Amylase, U/L	42
LDH, U/L	156
Cholesterol, mg/dL	43
Triglycerides, mg/dL	21
CEA, ng/mL	0.963
ADA, IU/L	128.0
NT-proBNP, pg/mL	480
Tuberculosis tests	
M. tuberculosis PCR	Negative
AFB smear	Negative

WBC = white blood cell, RBC = red blood cell, LDH = lactate dehydrogenase, CEA = carcinoembryonic antigen, ADA = adenosine deaminase, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, PCR = polymerase chain reaction, AFB = acid-fast bacilli.

DIFFERENTIAL DIAGNOSIS OF LYMPHO-DOMINANT EXUDATE WITH HIGH ADENOSINE DEAMINASE LEVEL

Dr. Jong Min Lee: ADA is an enzyme that acts as a hydrolase, converting adenosine to inosine and ammonia. Because it is produced during the activation of T lymphocytes, ADA levels in pleural fluid indirectly provide insights of the cellular immune response by T lymphocytes, making it a convenient tool for clinical diagnosis.

Tuberculous pleuritis is considered as a priority in differential diagnosis of disease with lympho-dominant exudate and high ADA level.[1] When the TB bacteria cause inflammation in the pleura, CD4 positive T lymphocytes and macrophages activate the cellular immune system and ADA is produced in the process. Because Korea is a country with relatively high prevalence of TB infection, patients with pleural effusion characterized by lympho-dominant exudate with high ADA level should be considered as possible tuberculous pleuritis. The decision to start empirical anti-TB treatment can be based on the combination of pleural ADA level and other clinical information.

Many other diseases, on the other hand, can increase the level of ADA in pleural fluid, especially those that activate T lymphocytes-mediated immune system. Malignant effusion can show lympho-dominant exudate feature with ADA elevation, and several autoimmune diseases related to T lymphocyte can show pleural effusion with high ADA levels when pleura is involved. Furthermore, some of parapneumonic effusions, which are less likely to show lympho-dominant feature, can also show ADA elevation.

Comprehensive approach considering both laboratory results and other clinical findings is crucial for differential diagnosis. Follow up sputum examination and efforts to find the pathogen are needed, and autoimmune studies should be done in this case scenario. Additionally, either percutaneous or surgical, biopsy plays important role in the diagnostic process.

PATHOLOGICAL FINDINGS

Dr. Jeong Hyeon Seong: The patient started empirical anti-TB treatment and was followed up in the outpatient department without drug compliance problem. However, approximately 7 months later, the patient developed dyspnea due to recurrent right pleural effusion, which prompted admission for further evaluation including pleural biopsy.

Repeated effusion analysis showed persistent lympho-dominant exudate with high level of ADA (130–150 IU/L) and the video-assisted thoracoscopic pleural biopsy of right pleura was performed (**Fig. 2**.). The result of histopathological examination showed fibroblast proliferation with chronic inflammatory cell infiltration and granulation tissues, and Ziehl-Neel stain showed no acid-fast bacilli present in the specimen. Tb/NTM real-time PCR test showed negative results for *M. tuberculosis* complex and non-tuberculous mycobacteria (NTM). These results did not align with the pathological features of tuberculous pleuritis.

Additional immunohistochemical staining was done; CD38 staining showed partially dense lymphoplasmacytic infiltration and immunoglobulin G (IgG) & IgG4 staining showed increased IgG4/IgG ratio more than 40% and more than 30 IgG4 positive plasma cell infiltration per high power field.

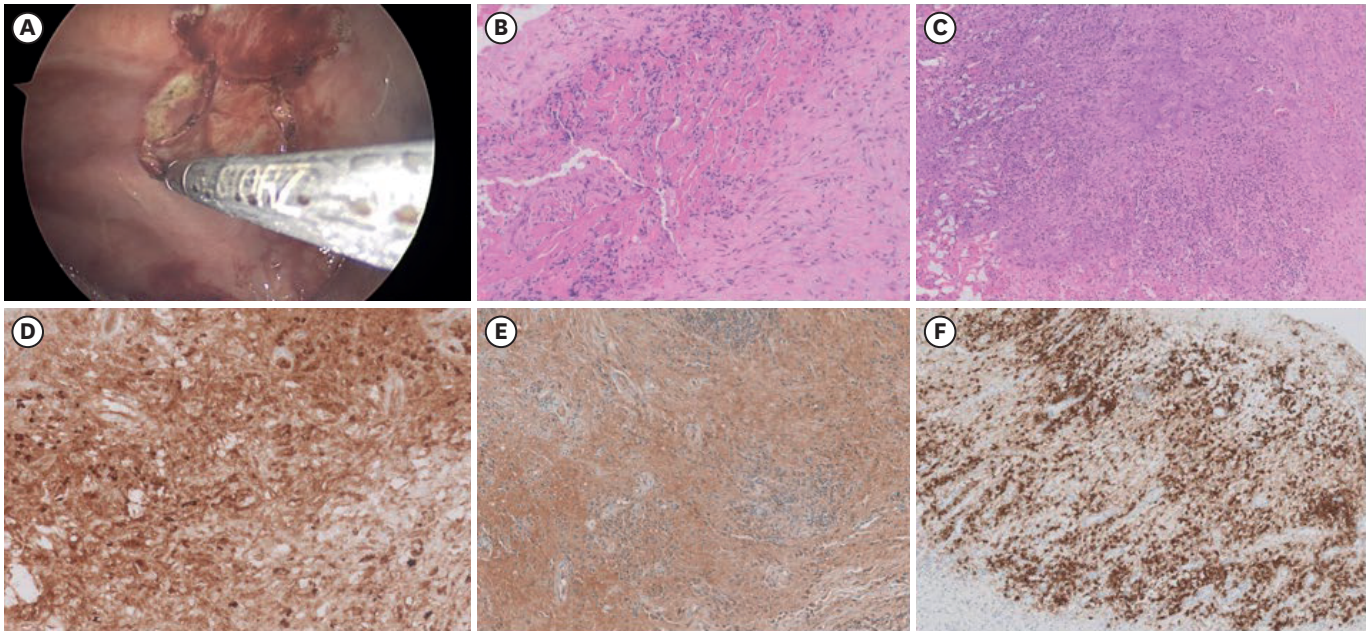

Fig. 2. Video-assisted thoracoscopic pleural biopsy and pathological findings. (**A**) Image of biopsy procedure at right pleura. (**B, C**) Histopathological findings showing fibroblasts and inflammatory cells, H&E stained. Immunohistochemical staining of immunoglobulin G (**D**), immunoglobulin G4 (**E**), and CD38 positive plasma cells (**F**).
H&E = haemotoxylin and eosin.

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AUTOIMMUNE STUDY

Dr. Jeong Hyeon Seong: In autoimmune study, anti-nuclear antibody (ANA) was positive with titer of 1:80 and with a cytoplasmic pattern, and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) was positive with titer of 1:80. However, all other autoimmune antibody test showed negative findings.

Serum eosinophil count was within normal range (0.35×10^9/L), and the serum total IgE level was elevated (2,455.7 IU/mL). Serum IgG level was within normal range (1,556 mg/dL) but serum IgG4 level was elevated to 745.75 mg/dL (**Table 3**).

Table 3. Autoimmune study findings

Variables	Results	Reference range
Parameters		
RA factor, qual.	Negative	Negative
Anti-CCP Ab, U/mL	Negative	Negative (< 5)
Anti ds-DNA Ab, IU/mL	Negative (19.9)	Negative (< 27)
ANA	Positive (1:80, cytoplasmic)	Negative
ANCA	Positive (1:80, pANCA)	Negative
Anti-MPO Ab, CU	Negative	Negative
Anti-PR3 Ab, CU	Negative	Negative (< 5)
Anti-DNA Ab, IU/mL	1.03	0.00–7.00
IgG, mg/dL	1,556	700–1,600
IgG4, subclass, mg/dL	745.75▲	3.9–86.4
IgM, mg/dL	71	40–230
C3, mg/dL	108	90–180
C4, mg/dL	30.8	10–40
Anti-ENA/DNA (multiplex)		
SS-A 52	Negative	Negative
SS-A 60	Negative	Negative
SS-B	Negative	Negative
Sm	Negative	Negative
RNP/Sm	Negative	Negative
Scl-70	Negative	Negative
Centromere B	Negative	Negative
Ribosomal P	Negative	Negative
Jo-1	Negative	Negative
PM-Scl	Negative	Negative
PCNA	Negative	Negative
Nucleosomes	Negative	Negative
Histones	Negative	Negative
AMA M2	Negative	Negative
Eosinophilia evaluation		
Eosinophil count, 10^9/L	0.35	0.05-0.35
Mast serum IgE test, IU/mL	< 1.0, class 0	< 1.0, class 0
Total IgE, IU/mL	2,455.7▲	0–158
Micro-ELISA test	Negative	Negative
Toxocariosis IgG (index)	Negative (0.48)	Negative (< 1.0)

Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Seoul St. Mary's Hospital are for adults who do not have medical conditions that could affect the results.
RA = rheumatoid arthritis, CCP = cyclic citrullinated peptide, Ab = antibody, ANA = anti-nuclear antibody, ANCA = antineutrophil cytoplasmic antibodies, MPO = myeloperoxidase, PR3 = proteinase 3, IgG = immunoglobulin G, IgM = immunoglobulin M, ENA = extractable nuclear antigen, IgE = immunoglobulin E, ELISA = enzyme-linked immunosorbent assay.

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FINAL DIAGNOSIS

Dr. Jeong Hyeon Seong: Based on the serum IgG4 level elevation and pathological findings, IgG4 related disease with pleural involvement was diagnosed.

GENERAL INTRODUCTION OF THE DISEASE MANAGEMENT

Dr. Hyeong Jun Cho: IgG4-related disease is an autoimmune condition characterized by immune-mediated inflammatory fibrosis, which is driven by the activation of CD4+ cytotoxic T lymphocytes. It typically manifests as tumor-like mass lesions that can affect nearly any organ in the body.[2] It is essential to distinguish it from malignancies and other similar conditions to avoid unnecessary surgery. The diagnosis process often relies not only on serum IgG4 levels but also on pathological confirmation through tissue biopsies. Pathological findings may include the presence of IgG4-positive plasma cells and lymphocyte infiltration, storiform fibrosis, and obliterative phlebitis.[3]

The initial treatment of choice is glucocorticoids,[2] with an initial dose of oral prednisolone 0.6 mg/kg/day. To minimize potential side effects, the initial dose is typically administered for about 2 to 4 weeks, and the dose is gradually tapered based on the patient's response, with the goal of discontinuing the medication within three years. It's worth noting that around 40% of patients may not achieve complete remission or may experience a relapse within one year after stopping glucocorticoid treatment. In such cases, re-administration of steroids or dose escalation is often effective, and, in some cases, the addition of azathioprine may be considered.

DISCUSSION

Dr. Hyeong Jun Cho: This case presents a remarkably rare clinical manifestation (pleural involvement) of IgG4-related disease, which is uncommon disease. Since IgG4-related disease is known as a systemic disease, were there any other organs aside from the pleura that showed involvement?

Dr. Jong Min Lee: IgG4-related disease is a systemic condition that can potentially involve nearly any organ in the body. The frequency of organ involvement may vary, and the disease often presents in forms like type 1 autoimmune pancreatitis, retroperitoneal fibrosis, or enlargement of the lacrimal and salivary glands, which are more commonly recognized manifestations.[2]

In this case, the pleural involvement leading to pleural effusion was observed, and the diagnosis was made following a comprehensive evaluation. The imaging and other tests performed did not reveal involvement of other organs beyond the pleura.

Dr. Yu Jin Hong: It seems that you decided to use empiric anti-TB treatment based on the elevated pleural ADA levels and later, steroid treatment was added following the tissue biopsy and confirmation of IgG4-related disease. The question arises as to whether this was a concurrent case of TB pleurisy or not.

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Dr. Jong Min Lee: Typically, when a patient present with unilateral pleural effusion, thoracentesis is performed to obtain fluid for analysis. Even if it's a case of tuberculous effusion, AFB smear, TB PCR, and culture tests on sputum or effusion can yield negative results.

Therefore, in cases where TB is suspected, especially if there's a lympho-dominant exudate, an ADA test often plays the key role. The cutoff value for ADA is typically set at 70 U/L.[4] If the ADA level is above 70, it's considered "probable TB," and empiric anti-TB treatment may be considered. If the ADA level falls between 40 and 70, further evaluation is needed, considering the patient's medical history, clinical presentation, and potential alternative diagnoses.[5] In cases where the diagnosis remains uncertain, a pleural biopsy can provide valuable assistance in reaching a definitive diagnosis.[6]

Dr. Jinsoo Min: South Korea, being one of the countries with a high incidence of TB, has traditionally recommended starting empiric anti-TB treatment when ADA levels are elevated.[5] However, with the recent decrease in TB incidence[7] and an aging patient population, there's now a need for caution when using ADA as the sole diagnostic criterion due to a higher risk of false positives. The most crucial aspect of diagnosing TB is confirming the presence of the TB bacterium.[8] It's recommended to conduct histopathological examinations, and when necessary, perform mycobacterial culture and nucleic acid amplification tests on the tissue to provide more reliable results.

Dr. Jong Min Lee: In conclusion, it's challenging to definitively determine whether this patient had TB based solely on the test results. Although the pathogen was not confirmed, the ADA levels remained persistently elevated. Furthermore, the fact that TB treatment was already undergone for 7 months might have led to false negative result of the pleural biopsy. Additionally, the increase in pleural effusion during TB treatment after six months could be attributed to a paradoxical reaction, known as immune reconstitution inflammatory syndrome (IRIS), which is more frequent in extrapulmonary TB like TB pleurisy. Hence, it's challenging to make a conclusive determination that it was not TB. Nevertheless, IgG4-related disease was later confirmed, and after additional steroid treatment and the completion of TB treatment, the patient is currently undergoing outpatient follow-up without any recurrence of pleural effusion.

Dr. Seo Wan: For this case patient, the steroid was used when the IgG4-related disease was diagnosed, and the effusion improved afterward. Considering the anti-inflammatory effects of steroids, can steroid also be used in combination with the treatment of TB pleurisy?

Dr. Jong Min Lee: Several studies comparing anti-TB treatment with and without corticosteroids for TB pleurisy have been conducted in the past. A meta-analysis of six existing randomized controlled trials (RCTs) was published in the Cochrane Library in 2017.[9] In summary, corticosteroids were shown to have a modest effect in some RCTs, primarily in improving the initial symptoms caused by pleural effusion and shortening the time to effusion resolution. However, the quality of evidence for these outcomes was low.

The meta-analysis did not find significant benefits of corticosteroids in terms of mortality, residual pleural fluid volume after 8 weeks of treatment, prevention of pleural adhesions, or long-term lung function decline. Additionally, the corticosteroid group had a higher incidence of adverse events leading to drug discontinuation, and in human immunodeficiency virus (HIV)-infected patients, Kaposi's sarcoma was reported only in the corticosteroid group.

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In clinical practice, when pleural effusion is severe enough to cause symptoms, pleural drainage is often the primary approach for both treatment and evaluation. Therefore, the addition of corticosteroids may not provide substantial benefits and could potentially lead to adverse events. As a result, treatment guidelines for TB typically recommend the standard 6-month anti-TB regimen without the addition of steroids for TB pleurisy. Steroids are recommended as an adjunct treatment only in specific cases, such as TB meningitis. The use of corticosteroids for TB pericarditis has also been debated, with recent research showing no significant benefit, so their selective use is recommended depending on the circumstances.

Related questions

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