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C. P. C.： The 775th Clinicopathological Conference： A Case of Clinically Diagnosed Bronchiolitis Obliterans Complicated by Pulmonary Aspergillosis

Daisuke Takekoshi[1], Shiko Honma[2], Takako Kiyokawa[2], Yusuke Iteya[3], Masahide Imamura[3], Kentaro Hirai[3], Akari Moriyama[3], Megumi Tsujino[3], Chen Yisyuan[3], Keitaro Okuda[1], Hiromichi Hara[1], Takanori Numata[1], Shunsuke Minagawa[1], Jun Araya[1], and Kazuyoshi Kuwano[1]

[1]*Division of Respiratory Diseases, Department of Internal Medicine, The Jikei University School of Medicine*
[2]*Department of Pathology, The Jikei University School of Medicine*
[3]*Center for Postgraduate Medical Education, The Jikei University School of Medicine*

ABSTRACT

We report on a woman in her early 60s with follicular lymphoma in whom a severe obstructive ventilatory defect developed and was clinically attributed to bronchiolitis obliterans. The patient was treated with macrolide antibiotics, inhaled corticosteroids, and bronchodilators but responded only moderately. She was treated with steroid pulse therapy and nintedanib but showed no clinical response. The patient eventually died of pulmonary aspergillosis. The autopsy showed evidence of only infectious disease. Bronchiolitis obliterans is difficult to diagnose and refractory to treatment. Physicians should be aware of the disease entity for early diagnosis and careful treatment because "treatment" can result in significant harm.

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Key words： bronchiolitis obliterans, pulmonary aspergillosis, follicular lymphoma

Case

A woman in her early 60s noticed a bump in her neck and was evaluated at the Division of Clinical Oncology/Hematology, Department of Internal Medicine, of The Jikei University Hospital. Positron emission tomography/computed tomography (CT) revealed systemic lymphadenopathy consistent with lymphoma. A left axillary lymph node biopsy confirmed the diagnosis of follicular lymphoma. While undergoing these investigations, the patient reported a gradual onset of dyspnea on exertion.

Three and a half months later the patient was admitted to The Jikei University Hospital to begin receiving chemotherapy for the lymphoma. When the first round of a chemotherapy regimen with rituximab had been completed, she became acutely dyspneic, requiring low-flow supplemental oxygen to maintain oxygen saturation greater than 90%. Dyspnea and hypoxemia gradually subsided over several hours and were attributed to an infusion reaction. The patient was discharged after several days of uneventful observation. However, when the patient was admitted to the hospital 2 weeks later for a planned second round of chemotherapy, dyspnea during exertion had worsened, and oxygen desaturation during exertion became evident. Because of these symptoms, the patient was referred to the Division of Respiratory Diseases of the Department of Internal Medicine.

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竹越大輔，本間志功，清川貴子，射手矢雄介，今村正秀，平井健太郎，森山　明，辻野　恵，陳苡瑄，奥田慶太郎，原　弘道，沼田尊功，皆川俊介，荒屋　潤，桑野和善
Mailing address： Daisuke Takekoshi, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo 105-8461, Japan
E-mail： takekoshi@jikei.ac.jp

While being evaluated by this division, the patient denied respiratory symptoms, such as coughing and sputum production, other than shortness of breath. She reported no precipitating events that might have led to dyspnea. She had no personal or family history of asthma or other respiratory diseases. The patient's family history was unremarkable. She had never smoked cigarettes and had no history of drug allergies. She worked at a desk as a civil servant in a city hall. She denied exposure to dust, chemicals, fungi, and animals, including pets and wild birds. Her medical history included serous otitis media, mastitis, glossitis, oral mucositis, and cranial bone fracture when she had been assaulted 24 years earlier.

The medications the patient was receiving included dexamethasone oral ointment, azulene sulfonate hydrate mouthwash, lidocaine mouthwash, olopatadine eye drops, and fluorometholone eye drops, which had first been given upon admission owing to glossitis and oral mucositis. Trimethoprim/sulfamethoxazole, acyclovir, and lansoprazole had been started as prophylactic agents for ulcerative diseases 1 day before rituximab was to be administered. Ibuprofen, chlorpheniramine maleate, and betamethasone had also been administered as premedications.

The results of examination were height, 151 cm ; weight, 48.8 kg ; body mass index, 21.4 kg/m^2 ; blood pressure, 129/72 mm Hg ; heart rate, 78 bpm ; temperature, 35.9°C ; and oxygen saturation, 96% at 3 L/minute through a nasal cannula. Auscultation of the chest found no rales. Results of physical examination of the other parts of the body were unremarkable, except for known cervical and axillary lymphadenopathy. The laboratory test results included a C-reactive protein level of 1.17 mg/dL (reference range, < 0.1 mg/dL) and a soluble interleukin 2R level of 1,570 U/mL (reference range, < 496 U/mL). The results of laboratory tests, including immunological and infectious tests, were unremarkable.

A CT examination that had been performed while the lymphoma was being investigated, 4 months before being referred to the Division of Respiratory Diseases, had not shown abnormalities in the lung field (Fig. 1A). However, when the patient had been referred, the bronchial/bronchiolar wall appeared slightly thickened and lung hyperinflation was apparent compared with the earlier CT examination (Fig. 1B). During expiration, the lungs failed to deflate, indicating air trapping (Fig. 1C).

Spirometry performed while the lymphoma was being investigated had results almost within the normal limits, but at the time of referral 3 months later spirometry showed a severe obstructive ventilatory defect (Fig. 2). The bronchodilator response test was unresponsive (data not shown).

On the basis of these findings, bronchiolitis obliterans (BO) associated with lymphoma was suspected. Although pathological findings were required for a definitive diagnosis, the limited respiratory function would have made lung biopsy unsafe. Therefore, to obtain additional supporting evidence we performed ventilation-perfusion lung scintigraphy, which demonstrated multiple severe ventilatory defects consistent with BO (Fig. 3). On the basis of these findings, a clinical diagnosis of BO was made.

CLINICAL COURSE

Respiratory therapy was begun with inhaled corticosteroids, a long-acting β_2 agonist, a long-acting muscarinic antagonist, and a low-dose macrolide (clarithromycin, 200 mg/day), in addition to the underlying lymphoma being treated. With these treatments, pulmonary function was slightly improved and stabilized (Fig. 4). However, because improvement plateaued at a low level, we decided to attempt steroid pulse therapy.

Although spirometry showed no improvements after steroid pulse therapy (Fig. 4), X-ray images and CT images showed that a new development was a nodular lesion with surrounding ground-glass opacities (Fig. 5). The patient became febrile, and blood tests revealed elevated level of C-reactive protein. Treatment with tazobactum/piperacillin was started, but the response was poor. Micafungin was started empirically to treat possible fungal infections. The sputum culture was eventually positive for *Aspergillus* species, and voriconazole was administered instead of micafungin. On the basis of the acutely progressive lung infiltrate with sputum cultures positive for *Aspergillus* species in a patient who had undergone steroid pulse therapy, invasive pulmonary aspergillosis (IPA) was diagnosed.

After treatment with voriconazole had been started, the IPA was considered to have become clinically stabilized. However, the patient's respiratory condition gradually worsened and the arterial partial pressure of carbon dioxide ($PaCO_2$) increased to > 50 mm Hg. Respiratory support at night was started with a noninvasive positive pressure ventilator.

Table 1. Laboratory data

Variable	Reference range	At referral
Hemoglobin (g/dL)	11.6–14.8	14.0
White blood cells (per μL)	5500–8600	6500
Differential count (%)		
Neutrophils	40.6–76.4	78.9
Lymphocytes	16.5–49.5	11.6
Monocytes	2.0–10.0	6.6
Eosinophils	0.0–8.5	2.0
Platelets (× 103 per μL)	158–348	318
Aspartate aminotransferase (IU/L)	13–30	15
Alanine aminotransferase (IU/L)	7–23	9
Lactate dehydrogenase (IU/L)	124–222	203
Total bilirubin (mg/dL)	0.4–1.5	0.7
γ Glutamyl transpeptidase (IU/L)	9–32	10
Total protein (g/dL)	6.6–8.1	7.0
Albumin (g/dL)	4.1–5.1	3.7
Amylase (IU/L)	44–132	57
Urea nitrogen (mg/dL)	8–20	13
Creatinine (mg/dL)	0.46–0.79	0.68
Uric acid (mg/dL)	2.6–5.5	2.6
Na (mmol/dL)	138–145	142
K (mmol/dL)	3.6–4.8	4.4
Cl (mmol/dL)	101–108	99
Ca (mg/dL)	8.8–10.1	10.1
C-reactive protein (mg/dL)	<0.15	1.17
Brain-type natriuretic peptide (pg/mL)	<18.5	14.2
Krebs von den Lungen antigen (U/mL)	<500	244
Surfactant protein D (ng/mL)	<110	17.2
Aspergillus antigen	Negative	Negative
C10/11 cytomegalovirus antigen (positive cells/150,000 cells)	0	0
β-D glucan (pg/mL)	<11	<6.0
Candida antigen		Negative
T-SPOT.*TB*™ assay	Negative	Negative
SARS-CoV-2 polymerase chain reaction	Negative	Negative
Soluble interleukin 2 receptor (U/mL)	122–496	1570
Immunoglobulins		
IgG (mg/dL)	861–1747	878
IgA (mg/dL)	93–393	167
IgM (mg/dL)	50–269	42
IgE (IU/mL)	<250	7
IgG4 (mg/dL)	11–121	13
Antinuclear antibody	<40	Negative
Anti-cyclic citrullinated peptide antibody (U/mL)	<4.5	0.8
Anti-Sjogren's syndrome A antibody (U/mL)	<10	<1.0
Anti-Sjogren's syndrome B antibody (U/mL)	<10	<1.0
Anti-histidyl t-RNA synthetase (Jo-1) antibody (U/mL)	<10	<1.0
Anti-Smith antibody (U/mL)	<10	<1.0
Anti-ribonucleoprotein antibody (U/mL)	<10	<1.0
Anti-double-stranded DNA antibody (IU/mL)	<13	Negative
Anti-centromere antibody	<10	Negative
Myeloperoxidase-specific antineutrophil cytoplasmic antibody (U/mL)	<3.5	<1.0
Proteinase 3-specific antineutrophil cytoplasmic antibody (U/mL)	<3.5	<1.0

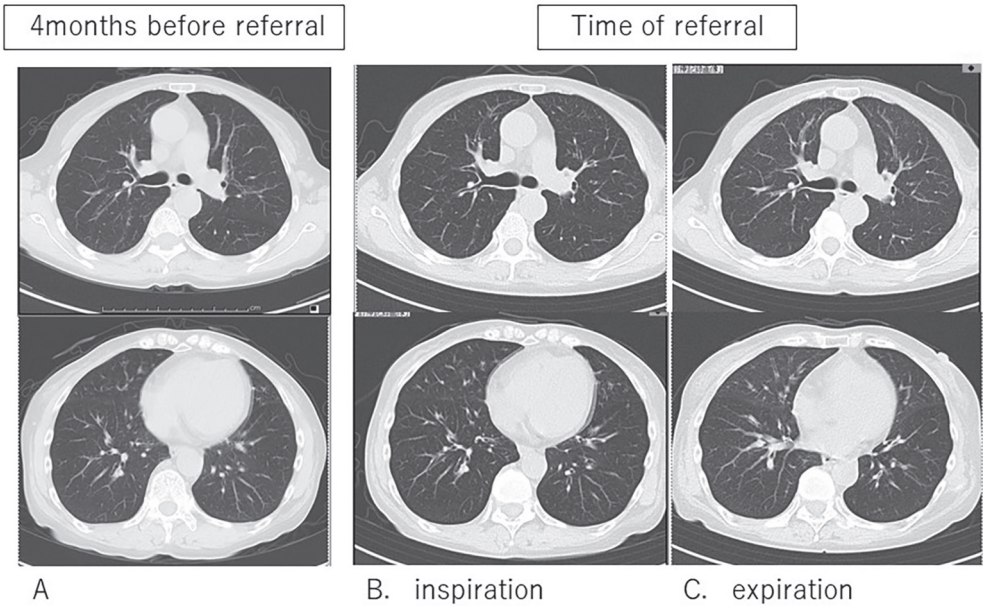

Fig. 1. Four months before referral to the Division of Respiratory Diseases, no abnormalities were observed in the lung field (A). At the time of referral, inspiration (B) and expiration (C) images were shown. The bronchial/bronchiolar wall was slightly thickened compared with before referral (A). The diameter of the anteroposterior had increased, and the lung field in B was hyperlucent, suggesting hyperinflation. The lungs did not deflate in C, which reflects air-trapping.

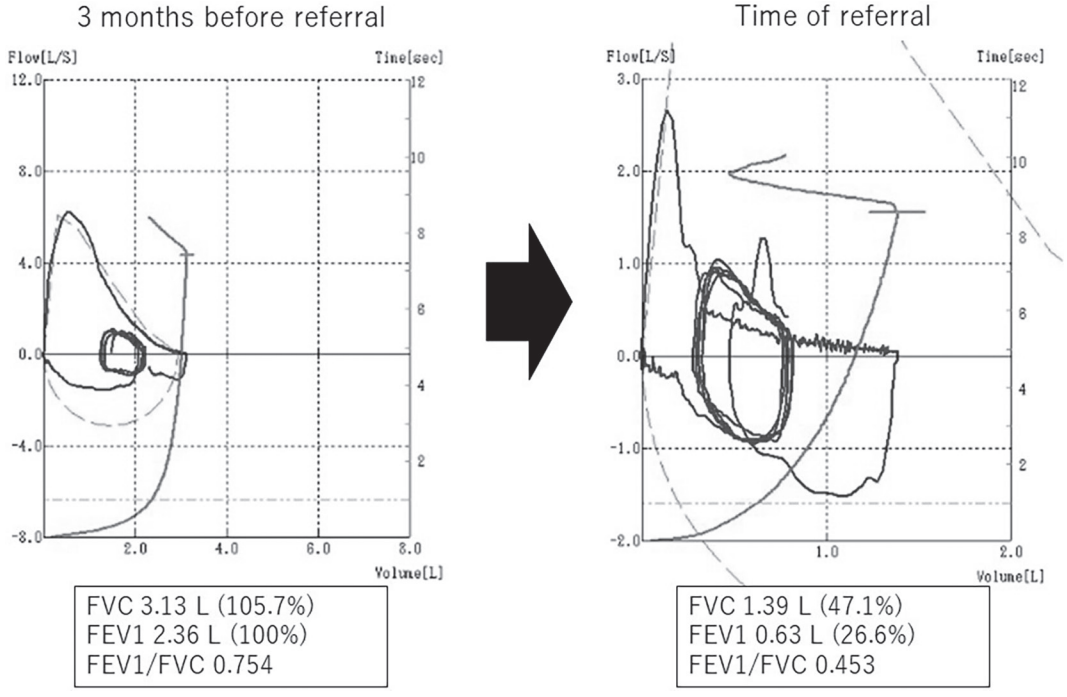

Fig. 2. Changes in spirometry at the time of referral to the Division of Respiratory Diseases. Three months before referral, the results of spirometry were almost normal. However, at the time of referral, the flow volume curve was convex down to a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) of 45.3%, representing a severe obstructive ventilatory defect.
V-V = volume-to-volume ratio

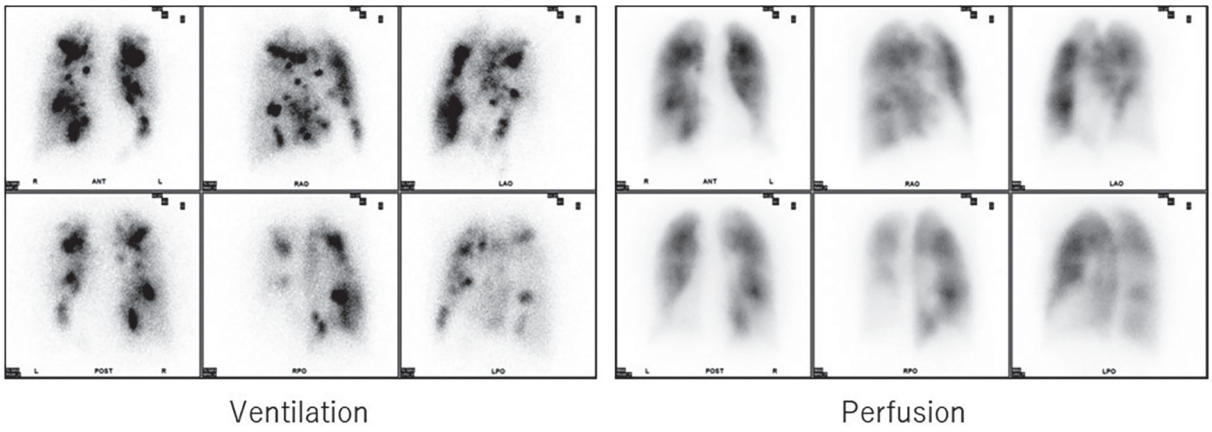

Fig. 3. The ventilation-perfusion scan demonstrated matched severe ventilation and perfusion defects.

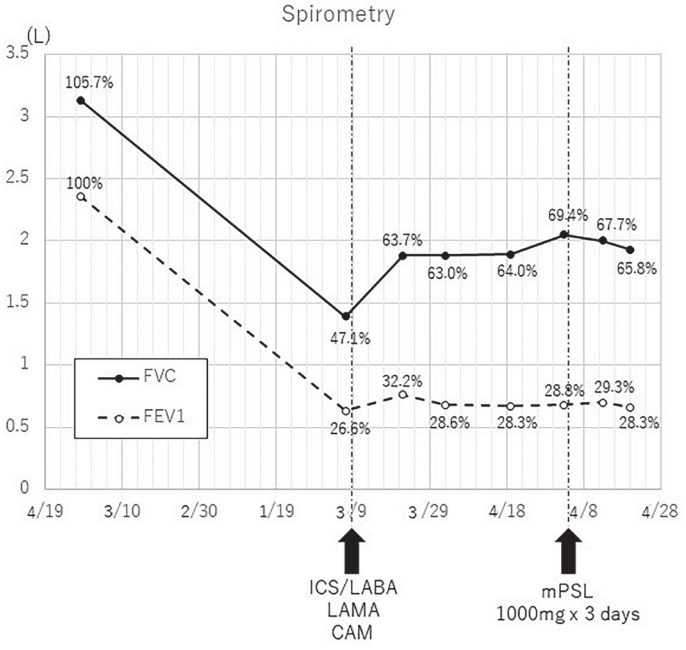

Fig. 4. Spirometry time course. The forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) had recovered modestly after the start of treatment with inhaled corticosteroids (ICS), a long-acting β_2-agonist (LABA), a long-acting muscarinic antagonist (LAMA), and clarithromycin. Recovery then plateaued. No response to steroid pulse therapy was observed.

To reduce the severity of small airway fibrosis and obstruction, thus improving the symptoms of BO, nintedanib has been used[1]. Therefore, the patient was treated with nintedanib for 3 weeks ; unfortunately, nausea and anorexia developed, and the respiratory status did not improve. The respiratory condition slowly but steadily decreased to a point where the patient could not undergo spirometry. The $PaCO_2$ had increased to 60 mm Hg are more by 2 months after steroid pulse therapy and 90 mm Hg or more by 3 months. Therefore, she began to receive only palliative care and died approximately 4 months after receiving steroid pulse therapy.

Autopsy Findings

An autopsy was performed 13 hours after the patient's death. The body was emaciated, with a height of 170 cm, weight of 38.7 kg, and a body mass index of 13.4 kg/m^2. In

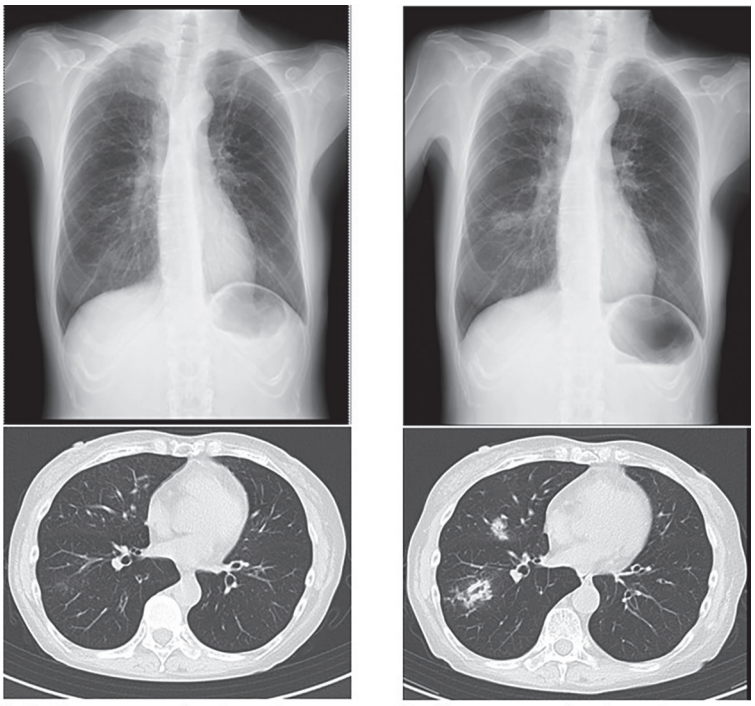

Fig. 5. Chest X-ray and computed tomographic images before and after steroid pulse therapy. The chest X-ray revealed new opacities on both sides of the lung. The computed tomographic images revealed multiple nodular lesions with surrounding ground-glass opacities.

the thorax, little pleural effusion and no pleural adhesions were observed. On gross examination, both lungs were mildly overweight (left, 289 g ; right, 416 g). In the cut sections, both lungs were slightly congested, and 2 cavitary lesions measuring 15 mm in the largest dimension contained blood, necrotic debris (Fig. 6B), and multiple yellowish-white nodules (1.2 cm in the largest dimension) surrounded by consolidation (Fig. 6A). The bilateral pulmonary apices had areas of consolidation, and the left upper lobe contained multiple dot-like consolidations (Fig. 6A). The heart weighed 422 g, the left ventricle was hypertrophic (thickness, 13 mm), and the right ventricle was mildly dilated. The aortic valve appeared normal, and the orifice of the tricuspid valve was dilated (circumference, 120 mm) (Fig. 6D and 6E). The liver weighed 1,039 g, and its cut surface showed chronic congestion with the so-called "nutmeg" appearance (Fig. 6C). The spleen (109 g) and both kidneys (left, 194 g ; right, 167 g) were congested. No lymphadenopathy was observed.

Microscopic examination showed that the pulmonary cavitary lesions consisted of fungal aggregates surrounded by epithelioid granulomas and fibrosis (Fig. 7A). Grocott's stain showed that the fungi had septate hyphae with sharp-angled branching and conidial heads, characteristic of an *Aspergillus* species (Fig. 7B) ; therefore, the lesion could be called an aspergilloma. Although fungi had invaded the vascular wall, invasion into the vascular lumen was not observed (Fig. 7A and 7C). In the grossly recognized multiple nodules, fungi and necrotic debris accompanied by neutrophilic infiltration were surrounded by epithelioid granuloma and fibrosis (Fig. 7D). The lesions had obliterated air spaces and destroyed the bronchial and bronchiolar walls. Necrotizing and granulomatous bronchitis or bronchiolitis was surrounded by well-demarcated organizing pneumonia (Fig. 7E), consistent with the dissemination of fungal infection through air spaces. Also observed were organizing pneumonia in the pulmonary apices and bronchopneumonia in the right upper lobe. No findings were suggestive of BO in the lungs.

The autopsy revealed extensive pulmonary aspergillosis, focal bronchopneumonia, and organizing pneumonia (Table 2). Right-sided cardiac dilatation and congestion in multi-

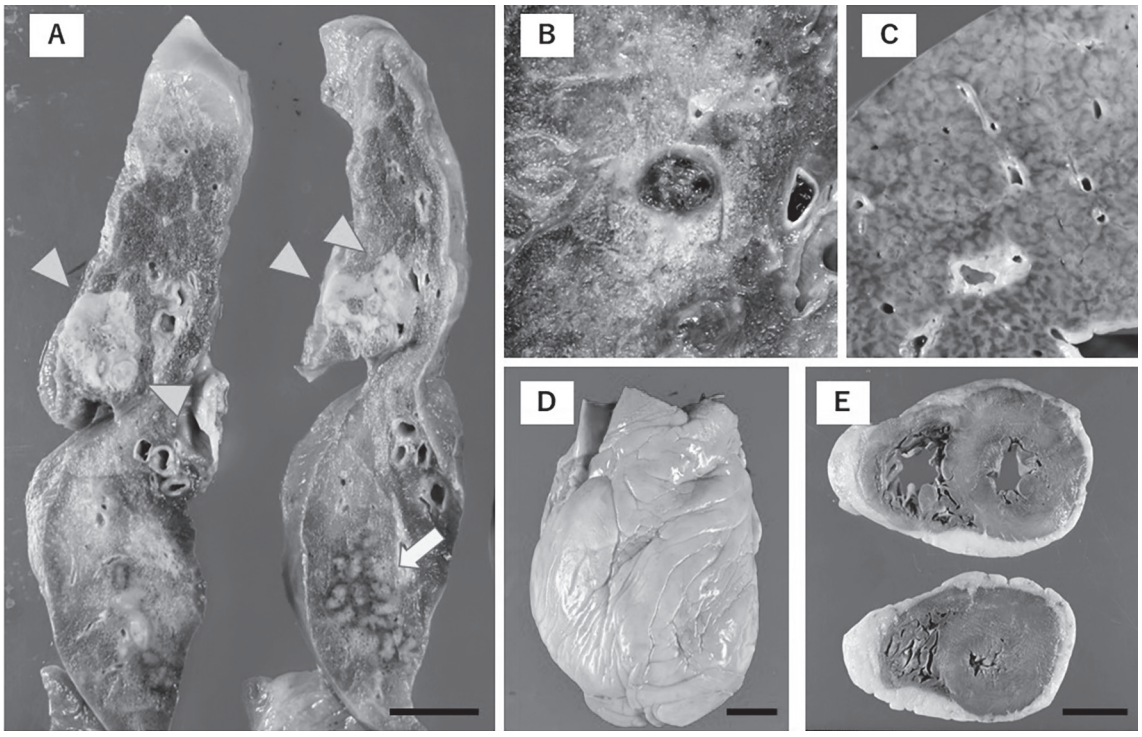

Fig. 6. Gross findings of organs at autopsy. A. Cut sections of the left lung showing multiple yellowish-white nodules (arrowhead) surrounded by consolidation and multiple dot-like consolidations (arrow). Scale bars, 2 cm. B. Pulmonary aspergilloma. C. The liver shows centrilobular congestion, a so-called "nutmeg" appearance. D, E. The heart showed concentric left ventricular hypertrophy and a mildly dilatated right ventricle. Scale bars, 2 cm in both figures.

ple organs suggested pulmonary hypertension. Left-sided concentric cardiomegaly reflected systemic hypertension. No evidence was found of recurrent follicular lymphoma. The cause of death was respiratory failure. An immunocompromised status based on hematological malignancy, immunosuppressive treatment, or malnutrition is believed to be the cause of extensive pulmonary aspergillosis.

Discussion

When the patient was referred to the Division of Respiratory Diseases, we concluded, on the basis of her history and the results of a physical examination, imaging studies, and spirometry, that the worsening dyspnea was due to a severe obstructive ventilatory defect. Obstructive ventilatory defects are caused by airway diseases, such as asthma, chronic obstructive pulmonary disease, diffuse panbronchiolitis, and BO. Such diseases as sarcoidosis, lymphoproliferative disorders, immunoglobulin G4-related lung disease, and amyloidosis can involve the airways and cause obstructive ventilatory defects. However, these defects are rarely caused by these diseases.

An extremely severe obstructive ventilatory defect that did not respond to a bronchodilator had developed in the present patient, a previously healthy never-smoking woman in her early 60s in whom lymphoma had recently been diagnosed. This clinical picture strongly points to the diagnosis of BO among the possible causes of obstructive ventilatory defects.

The rare disease of BO is characterized by subepithelial inflammation, fibrotic narrowing, and obliteration of the membranous bronchioles[2,3]. Small airway obstructions cause airflow limitations and air trapping. Spirometry has been used to demonstrate obstructive ventilatory defects. At an early stage, BO is often asymptomatic. As BO progresses, dyspnea on exertion and nonproductive cough develop. Bronchiectasis central to obstruction, pneumothorax, and pneumomediastinum due to high thoracic pressure secondary to hyperinflation can develop, and recurrent infections can complicate the clinical course. With further progression of BO, patients die of these complications or of respiratory failure[2,3].

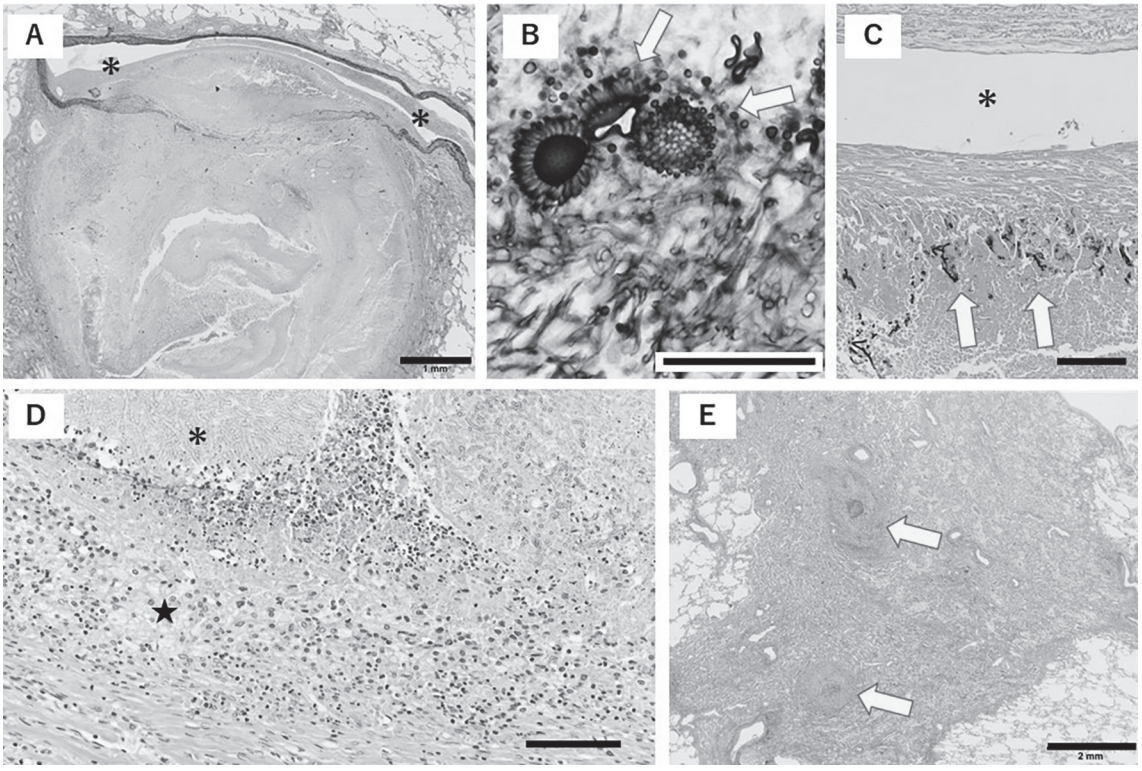

Fig. 7. Microscopic images of the lung at autopsy. A. Aspergilloma expanded into the pulmonary artery (asterisk). Elastica-Van Gieson stain. Scale bar, 1 mm. B. Grocott's stain highlighted *Aspergillus* hyphae with conidial heads (arrows) in aspergilloma. Scale bar, 50 μm. C. *Aspergillus* hyphae (arrows) are fragmented in the pulmonary artery wall (asterisk). Grocott's stain ; Scale bar, 100 μm. D. Necrotizing and granulomatous bronchiolitis consisted of fungal hyphae (asterisk) and necrotic debris accompanied by neutrophils surrounded by epithelioid granuloma (star) and fibrosis. Hematoxylin and eosin stain. Scale bar, 100 μm. E. Necrotizing and granulomatous bronchiolitis (arrows) surrounded by well-demarcated organizing pneumonia. Masson trichrome stain. Scale bar, 2 mm.

Table 2. Pathological diagnoses

1. Pulmonary aspergillosis and organizing pneumonia
1-1. Pulmonary aspergillosis, mainly subacute invasive pulmonary aspergillosis
1-2. Bronchopneumonia
1-3. Organizing pneumonia
2. No evidence of residual follicular lymphoma status after chemotherapy
3. Cardiac hypertrophy and evidence of right-sided heart burden
3-1. Concentric hypertrophy of the left ventricle
3-2. Dilation of the right ventricle, mild
3-3. Multiorgan congestion : liver, spleen, kidney
4. Emaciation

The pathogenesis of BO is unknown, but certain injuries to small airway epithelial cells and subepithelial structures are believed to induce abnormal repair mechanisms and lead to excessive fibrosis and airway obstruction. With the development of BO, many conditions and agents are associated (Table 3). Given this list, an abnormal immunological mechanism has been proposed, but little is known about its cellular and molecular pathogenesis[2,3].

At an early stage in cases of BO, the radiographic findings of the chest are usually normal. As the disease progresses, symptoms might be found that are consistent with hyperinflation, such as a low and flattened diaphragm, hyperlucency of the lung, and widening of the retrosternal space in the lateral view[2,3]. Small-airway lesions in BO are not large enough to be visible, even in CT images. Instead, the main radiographic finding in the present case was a mosaic pattern secondary to air trapping and bronchiectasis with thickening of the bronchial wall in the middle to central zone bronchi. Mosaic patterns can be enlarged through expiration. However, similar to what occurred in our patient, if air trapping is diffuse and the whole lung does not deflate, the mosaic pattern might not be observed. Ventilation-perfusion lung scintigraphy can help the diagnosis of

BO be made, even without abnormalities being observed with CT. Typically, a ventilation-perfusion scan demonstrates multiple matched ventilation defects[3] (Fig. 3).

For a definitive diagnosis of BO, a histopathological examination is required. A typical pathological finding in cases of BO is constrictive bronchiolitis. However, obtaining tissue samples is often difficult in suspected cases of BO because patients typically have a limited respiratory reserve, as did the present patient. Therefore, to further support the diagnosis of BO we performed a ventilation-perfusion scan.

No diagnostic criteria for BO are universally accepted. However, in Japan, the diagnostic criteria proposed by the Ministry of Health, Labour and Welfare in 2014 are often referred to (Table 4)[2]. The criteria consist of 3 domains : domain A, clinical symptoms ; domain B, diagnostic tests ; and domain C, differential diagnosis. A definitive diagnosis of BO is made if a symptom of domain A is present, if imaging and physiological test results and the histopathological findings are consistent with domain B, and if other specific diseases in domain C are excluded. A probable diagnosis is made if all criteria for a definitive diagnosis are present, but the histopathological findings from domain B are not met. The criteria are intended to diagnose "idiopathic" BO. Therefore, the criteria require the exclusion of specific diseases in domain C. In clinical practice, the criteria are used to diagnose BO in general by omitting domain C requirements.

In the present case, the patient presented with dyspnea during exertion (domain A). A CT examination showed air trapping, and spirometry revealed an obstructive ventilatory defect (domain B). Therefore, BO was clinically diagnosed. Because symptoms had developed before the start of chemotherapy, lymphoma-associated BO was diagnosed.

No treatment options have been established in clinical trials due to the rarity of BO[3], but some treatments have been attempted. Therefore, treatment is guided by theories, biological research, and anecdotal experiences[3,4]. The treat-

Table 3. Causes of bronchiolitis obliterans (Respir Invest 2021 ; 59 : 8)

Categories	
Transplantation (rejection, graft versus host disease	Lung transplantation Bone marrow transplantation
Systemic connective tissue diseases	Rheumatoid arthritis Sjogren's syndrome Lichen planus Systemic lupus erythematosus Eosinophilic fasciitis Systemic sclerosis Ankylosing spondylitis
Paraneoplastic syndrome	Paraneoplastic pemphigus Malignant lymphomas Castleman disease Lichen planus
Inflammatory bowel disease	Inflammatory bowel disease
Stevens-Johnson syndrome	Stevens-Johnson syndrome
Dietary supplement	*Sauropus androgynus* ingestion
Organizing infectious exudates	Adenoviruses Respiratory syncytial virus Influenza virus Measles virus Mycoplasma Nitrogen oxide (silo-filler's disease)
Chemical fume inhalation	Diacetyl (popcorn lung) Thionyl chloride (lithium battery production) Phosgene/sulfur mustard (chemical warfare gases) Fire fumes
Idiopathic	

Table 4. Diagnostic criteria for idiopathic bronchiolitis obliterans (Ministry of Health, Labour and Welfare, 2014)

Domain A : clinical symptoms
1. Dyspnea on exertion 2. Cough 3. Sputum production
Domain B : diagnostic tests
1. Imaging The chest X-ray film shows an almost normal or slightly hyperinflated lung. Inspiratory and expiratory high-resolution computed tomography reveals air trapping. 2. Physiological tests Pulmonary function test shows an obstructive ventilatory defect. 3. Pathological findings The lung biopsy shows a patchy distribution of submucosal or peribronchiolar fibrosis/scaring at the bronchiolar level.
Domain C : differential diagnosis
Exclude the diseases and specific causes listed below : Diffuse panbronchiolitis, chronic obstructive pulmonary disease, bronchial asthma, interstitial lung disease, inhalation of volatile gases, and connective tissue diseases.
Diagnosis Definite diagnosis : item 1 of domain A + item 3 of domain B + Exclude all conditions listed in Domain C Probable diagnosis : Item 1 from domain A + Items 1 and 2 from domain B + Exclude all conditions listed in Domain C

ment options usually attempted are anti-inflammatory agents, the treatment of ventilatory defects, the treatment of respiratory failure, and antifibrotic agents (Table 5)[3]. Consequently, we first treated the patient with inhaled corticosteroids, a long-acting β_2-agonist, a long-acting muscarinic antagonist, and low-dose macrolides. However, the improvement was limited, and we decided to attempt steroid pulse therapy, which, unfortunately, led to pulmonary aspergillosis.

Pulmonary aspergillosis is divided into 3 categories : allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, and IPA. In the present case, the lung lesions progressed over a few days, and we believe that the patient had IPA.

Being an opportunistic infection, IPA occurs in immunocompromised patients. Patients at high-risk for IPA include those with severely depressed immune systems, such as those with hematologic malignancy or severe neutropenia and those undergoing steroid pulse therapy. In patients with an underlying severe lung disease, even with modest systemic immunosuppression, IPA can develop owing to these patients' locally compromised immune system. Because IPA can progress rapidly, even over the course of several hours, early diagnosis and treatment are important. A case of IPA is suspected if patients at high risk have pneumonic symptoms, an elevated inflammatory response on blood tests, and CT findings consistent with IPA. The clinical diagnosis of IPA is confirmed if a patient has elevated serologic tests or pathological findings and is definitive if an *Aspergillus* species grows in culture[5].

Table 5. Treatment options for bronchiolitis obliterans (Respir Invest 2021 ; 59 : 8)

Anti-inflammatory treatment in the early phase and acute exacerbations Glucocorticoid Immunosuppressant Immunomodulator (macrolides)
Treatment of obstructive ventilatory defects Bronchodilators
Treatment for respiratory failure Supplemental oxygen Noninvasive positive pressure ventilation
Antifibrotic treatment Nintedanib Pirfenidone

Empirical treatment options for patients with IPA include voriconazole, liposomal amphotericin B, itraconazole, caspofungin, and micafungin. The targeted treatment options include voriconazole and liposomal amphotericin B[5].

In the present patient, BO was clinically diagnosed, but the autopsy did not provide pathological evidence. A possible reason for the lack of evidence is that the clinical diagnosis had been completely incorrect and that the patient did

not have BO, but given the clear clinical evidence of BO and the absence of alternative explanations for her symptoms (i.e., severe obstructive ventilatory defect), BO was unlikely to be completely absent. There are several possible explanations why pathological findings of BO were not found. First, because BO had been diagnosed and pulmonary aspergillosis had developed more than 3 months before the patient died, the BO lesions might have been masked by destructive *Aspergillus* invasion. A second explanation is that BO lesions are difficult to identify and can easily be overlooked. A third and final possible explanation is that BO lesions were modified with treatment and were difficult to identify.

We speculate that the first and second possible explanations are the major reasons why BO lesions could not be identified in the present patient. In other words, the destructive nature of *Aspergillus* infection makes BO lesions even more difficult to identify. The third possible explanation is unlikely, because the patient had ventilatory difficulties until the end of her life.

Conclusion

The disease of BO is difficult to diagnose and refractory to treatment. Physicians should be aware of BO for early diagnosis and be cautious about its treatment because, as in the present case, "treatment" is not without the risk of harm.

Authors have no conflict of interest.

Reference

1. Tang W, Yu T, Dong T, Liu T, Ji J. Nintedanib in bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation. Chest. 2020 ; 158 : e89–e91.
2. Bronchiolitis obliterans (in Japanese). Japan Intractable Diseases Information Center. https://www.nanbyou.or.jp/entry/4721. [accessed 2022–12–10]
3. Homma S, Ebina M, Kuwano K, Goto H, Sakai F, Sakamoto S, et al. Intractable diffuse pulmonary diseases : Manual for diagnosis and treatment. Respir Investig. 2021 ; 59 : 8–33.
4. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. N Engl J Med. 2014 ; 370 : 1820–8.
5. Guideline for Invasive Fungal Disease Creating Committee ed. Japanese Domestic Guidelines for the Management of Invasive Fungal Disease 2014 (Partial Update in Pediatrics) (in Japanese). Tokyo : Kyowa Kikaku ; 2014.