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Case Report

Rapidly progressive interstitial pneumonia associated with anti-NXP2 antibody secondary to malignancy

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ABSTRACT

The diagnosis of a diffuse lung disease is challenging for physicians and it requires a multidisciplinary team approach to solve this problem. Herein, we present a case of common bile duct obstruction from pancreatic ductal adenocarcinoma after biliary stent placement, which developed a rapidly progressive bilateral lung infiltration after oesophagogastroduodenoscopy. After a diagnostic evaluation based on clinical, radiographic, and pathological findings, a diagnosis of rapidly progressive interstitial pneumonia associated with anti-nuclear matrix protein (NXP) 2 antibody secondary to malignancy was made. In patients with interstitial lung disease with unclear aetiologies, autoantibodies, including antinuclear antibody and myositis-specific antibodies should be evaluated, even if there are no clinical signs of autoimmune disease. Although this is the first case report of an acute interstitial pneumonitis-associated anti-NXP2 antibody, physicians should recognise this condition as it can rapidly cause acute fulminant respiratory failure.

Abbreviations

NXP	nuclear matrix protein
CBD	common bile duct
EGD	oesophagogastroduodenoscopy
CXR	chest radiograph
CT	computed tomography
FB	flexible bronchoscopy
BALF	bronchoalveolar lavage fluid
DAD	diffuse alveolar damage
ILD	interstitial lung disease

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IP	interstitial pneumonitis
AIP	acute interstitial pneumonitis
CTD	connective tissue disease
ANA	antinuclear antibody
DM	dermatomyositis
NSIP	nonspecific interstitial pneumonia
OP	organizing pneumonia
MSA/MAA	myositis specific and associated autoantibodies

1. Introduction

The diagnosis of a diffuse lung disease is a challenging task for physicians and requires a multidisciplinary approach to identify the cause of the disease. Herein, we present a rare case of rapidly progressive interstitial pneumonia associated with an anti-nuclear matrix protein (NXP) 2 antibody secondary to malignancy.

2. Case report

A 71-year-old woman was admitted to our hospital with a history of epigastric pain for 2 days. She was diagnosed with pancreatic ductal adenocarcinoma at the uncinate process, and had undergone endoscopic retrograde cholangiopancreatography with biliary stent placement 1 month prior due to a distal common bile duct (CBD) obstruction. Oral capecitabine was subsequently initiated 2 weeks before presentation.

On admission, an ascending cholangitis with CBD stent malposition was suspected. The patient was initially treated with intravenous ceftriaxone (2 g, daily).

Oesophagogastroduodenoscopy (EGD) was subsequently performed with a light intravenous sedation. A distal biliary stent migration was observed but remained in place. The stent was not retrieved, and the procedure was completed uneventfully.

The day after EGD, the patient developed a dry cough and low-grade fever. Chest radiography (CXR) demonstrated a new development of multifocal patchy and nodular consolidations, and ground-glass opacities in the left lung with a lower lung zone predominance (Fig. 1A–B). The antibiotic was subsequently changed to piperacillin/tazobactam. However, her symptoms rapidly deteriorated, and a progressive bilateral lung infiltration was demonstrated on CXR (Fig. 1C) after 1 week.

Physical examination revealed a body temperature of 36.8 °C, blood pressure of 160/80 mmHg, heart rate of 88 beats/min, respiratory rate of 24 breaths/min, and oxygen saturation of 90% while breathing room air. Pulmonary examination revealed fine inspiratory crackles bilaterally, predominantly in the lower left lung zone. Abdominal examination revealed mild epigastric tenderness. No abnormal cutaneous lesions or musculoskeletal abnormalities were noted.

The complete blood count showed leucocytosis (18,000 cells/mm³) with 78% neutrophils, 13% lymphocytes, 8% monocytes, normal platelets, and haemoglobin. Liver function test results were total bilirubin 2.3 mg/dL, direct bilirubin 2 mg/dL, and ALP 234 U/L. The other serum biochemistry test findings were all within the normal ranges.

All blood and sputum cultures were negative. The level of C-reactive protein was 148.98 mg/L and that of procalcitonin was 0.17 ng/mL. Computed tomography (CT) of the chest showed multifocal peribronchovascular consolidations and patchy ground-glass opacities with superimposed interlobular septal thickening and intralobular lines (Fig. 2A and B).

A flexible bronchoscopy (FB) was performed. A whitish turbid bronchoalveolar lavage fluid (BALF) was retrieved with no characteristics of a bile-like fluid. The BALF showed a white blood cell count of 488 cells/mm³ with 61% neutrophils and 39% monocytes. Bacterial, fungal and acid-fast bacilli staining and cultures of BALF were negative. The polymerase chain reaction tests to detect *Mycobacterium tuberculosis* and respiratory 33 pathogens were also negative. The BALF cytology and cell block were positive for malignant cells, consistent with metastatic adenocarcinoma and did not demonstrate bilirubin crystallisation (Fig. 2C). Histopathological examination of a transbronchial biopsy demonstrated organizing diffuse alveolar damage (DAD) (Fig. 2D) with no evidence of food particles or bile pigment.

Based on the rapidly deteriorating clinical course, chest CT findings, histopathology of DAD, and the exclusion of potential infections and chemotherapy-induced interstitial lung disease (capecitabine), acute interstitial pneumonitis (AIP) was diagnosed. Given the history of pancreatic adenocarcinoma, a connective tissue disease-related interstitial lung disease secondary to malignancy was suspected, despite the absence of cutaneous and musculoskeletal manifestations leading to the diagnosis. Further investigation of autoantibodies was conducted, which was negative for anti-nuclear antibody (ANA), whereas anti-NXP2 antibody was positive in the myositis profile-4 EUROLINE immunoblot assay (EUROIMMUN AG, Germany). Serum creatine kinase and aldolase were tested and the results were 12 U/L and 5 U/L, respectively. Thus, a diagnosis of rapidly progressive interstitial lung disease (ILD) associated with anti-NXP2 antibodies was confirmed.

The patient developed acute respiratory failure and sudden cardiac arrest 1 hr after FB. Cardiopulmonary resuscitation was performed, and the return of spontaneous circulation was achieved in 10 min. The left side pneumothorax was demonstrated on CXR, and left intercostal drainage was inserted. After the diagnosis was made, dexamethasone (15 mg/day) was administered intravenously. Continuous improvement of the lesion was observed on the follow-up CXR (Fig. 1D). However, owing to anoxic encephalopathy, the patient did not regain consciousness. After explaining the underlying advanced cancer and irreversible brain dam-

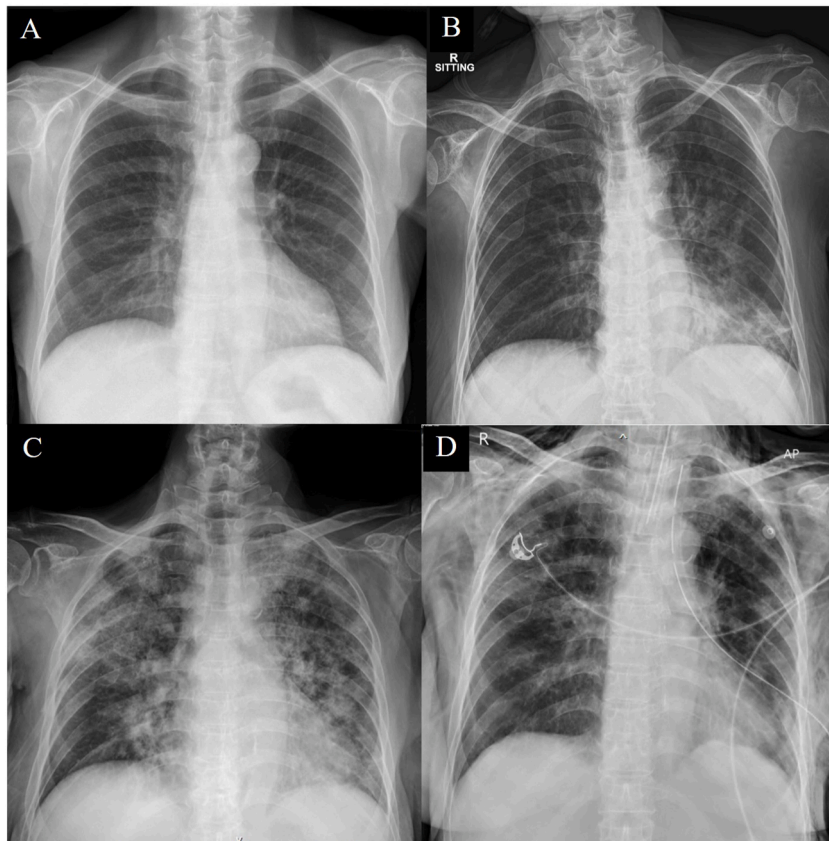


Fig. 1. Frontal chest radiographs (CXR) on the date of admission (A) and 1 day after oesophagogastrroduodenoscopy (EGD) (B) showing new development of multifocal patchy and nodular consolidations and ground-glass opacities in the left lung with a lower lung zone predominance. CXR obtained 1 week (C) after EGD showing interval progression of multifocal patchy and nodular consolidations and ground-glass opacities in both lungs. Follow-up CXR after treatment with dexamethasone for 1 week (D) showing interval resolution of multifocal consolidations and ground-glass opacities in both lungs.

age to her relatives, a decision was made to discontinue ventilatory support and all active treatments and palliate her. The patient died 1 week later.

3. Discussion

Bile acid is known as a cause of acute lung injury [1]. Bile acid-induced lung injury was initially suspected. Bile acid aspiration may occur due to aspiration during EGD or bronchobiliary fistula secondary to biliary obstruction [2]. Bile aspiration pneumonia was excluded after FB because of the absence of biliptysis, bilirubin crystals, and bile pigment.

Chemotherapy-induced ILD should be suspected when interstitial pneumonitis (IP) develops during the course of chemotherapy. Chemotherapeutic agents for pancreatic cancer such as gemcitabine, oxaliplatin, and nanoparticle albumin-bound paclitaxel have the potential to induce IP. However, in our patient, the sole chemotherapy provided was capecitabine which, to the best of our knowledge, has never been reported as a drug-induced IP unless in combination with other antineoplastic agents.

Lung metastasis can mimic ILD on chest radiography. Although metastatic pancreatic adenocarcinoma was discovered on the BALF cytology, this could not explain our patient's rapidly deteriorating clinical course.

The anti-NXP2 antibody, formerly known as anti-MJ, is considered a serologic marker of dermatomyositis (DM) and has been reported in DM, with a wide incidence ranging from 1.6 to 30%. Clinically, patients with anti-NXP2-positive DM have a higher prevalence of myalgia, dysphagia, peripheral oedema, and calcinosis than patients with anti-NXP2-negative DM [3,4]. In association with internal malignancies, 24–43% of patients with anti-NXP2-positive DM had malignancy which was found within 3 years after diagnosis [5].

ILD is a common manifestation in up to 32% of patients with DM, including patterns of usual interstitial pneumonia, non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), and AIP. In some cases, muscle and/or skin involvement may develop after ILD presentation, making this a diagnostic challenge. Clinicians should be aware of this disease entity when considering cases of isolated ILD of unclear aetiology, especially in those with a history of malignancy.

Our patient had no muscle involvement and no specific skin signs of DM but had ILD and positive anti-NXP2. Therefore, a diagnosis of DM has not yet been confirmed. However, there was no difference in survival between patients who fulfilled the Bohan and Pe-

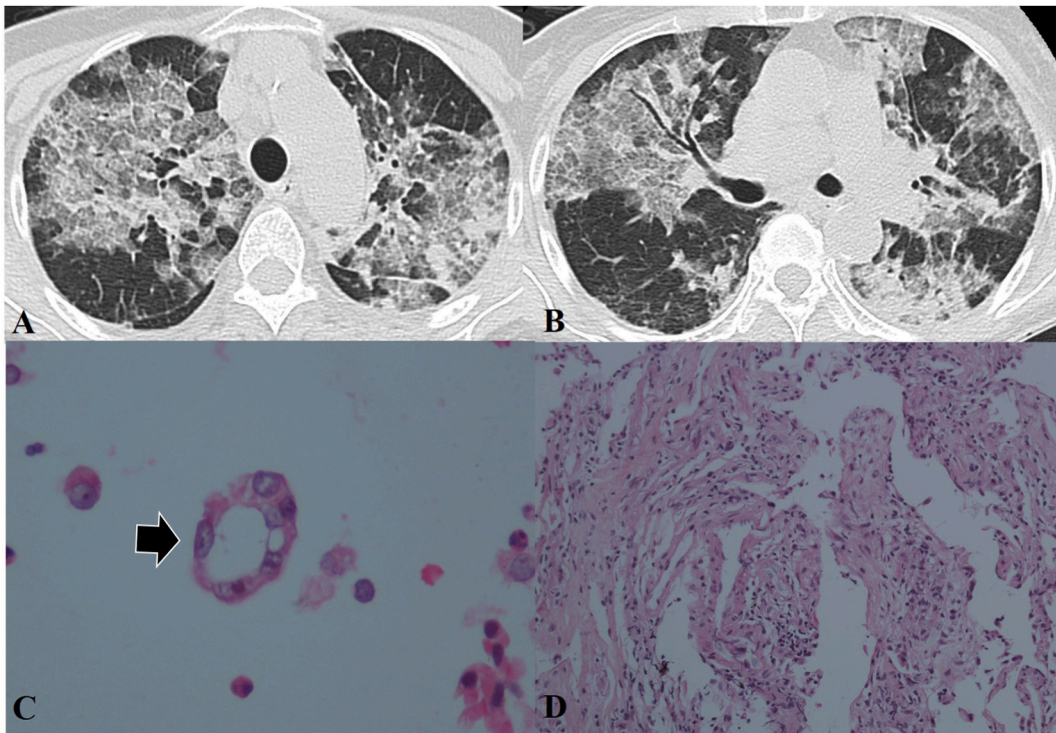


Fig. 2. Axial computed tomography (CT) of the chest in lung window (A–B) 1 week after oesophagogastroduodenoscopy showing multifocal peribronchovascular consolidations and patchy ground-glass opacities with superimposed interlobular septal thickening and intralobular lines (crazy-paving pattern). C. Histopathological findings (haematoxylin-eosin staining) from bronchoalveolar lavage fluid cell block showing clusters of neoplastic cells. These cells have large oval to irregular pleomorphic and hyperchromatic nuclei with vacuolated cytoplasm highly suggestive of adenocarcinoma. D. Histopathological findings (haematoxylin-eosin staining) from transbronchial lung biopsy showing interstitial inflammatory cells infiltration, fibroblasts proliferation, and pneumocyte type 2 hyperplasia with hyaline membranes compatible with organizing diffuse alveolar damage.

ter's criteria for inflammatory myopathies and those who had only ILD and positive myositis-specific and associated autoantibodies [6].

ILD associated anti-NXP-2 antibody is infrequent compared to other myositis-specific and associated autoantibodies (MSA/MAA) [3]. ILD patterns on CT images in previous reports were mostly NSIP and OP. To our knowledge, this is the first case report of DAD associated with anti-NXP-2 antibody.

Among DM-associated ILD, AIP has the worst prognosis due to its rapidly deteriorating clinical course and poor response to corticosteroid therapy. The treatment requires a combination of high-dose corticosteroids and immunosuppressive agents. Despite aggressive treatment, the mortality rate remains high.

4. Conclusion

Herein, we report a case of a rapidly progressive interstitial pneumonia associated with the anti-NXP2 antibody secondary to malignancy. In patients with ILD with unclear aetiologies, autoantibodies, including ANA and MSA/MAA, should be evaluated, even if there are no clinical signs of autoimmune disease as ILD may precede the clinical signs of CTD.

Contribution of each author

Nataphon Wuthithebuncha: took care of the patient, reviewed literature, and wrote the manuscript.

Viboon Boonsarnsuk: took care of the patient, reviewed literature, and wrote the manuscript.

Jakkrit Laikitmongkhon: took care of the patient and reviewed the manuscript.

Pimpin Incharoen: interpreted histological finding and reviewed the manuscript.

Warawut Sukkasem: interpreted radiographic finding and reviewed the manuscript.

Ethic and consent statement

This case report was approved by the Ethics Committee on Human Rights related to research involving human subjects at the Faculty of Medicine Ramathibodi Hospital. The written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Declaration of competing interest

All of the authors declare no competing interests.

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