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Pulmonary Alveolar Proteinosis-Like Pathological Changes Mimicking Lung Adenocarcinoma in Situ

Kazuki Hayasaka,[1] Tomohiro Fujita,[1] Shunsuke Eba,[1] Nobuyuki Sato,[1] Hidekachi Kurotaki[2] and Chihiro Inoue[3]

[1]Department of Thoracic Surgery, Aomori Prefectural Central Hospital, Aomori, Aomori, Japan
[2]Department of Pathology, Aomori Prefectural Central Hospital, Aomori, Aomori, Japan
[3]Department of Anatomic Pathology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

An enlarging ground-glass nodule (GGN) in the lungs closely resembles the characteristic appearance of a well differentiated lung adenocarcinoma or adenocarcinoma in situ (AIS). Herein, we present an unusual case characterized by clinical features suggestive of AIS but pathologically confirmed as exhibiting pulmonary alveolar proteinosis (PAP)-like changes. Patients with enlarging pure GGNs warrant consideration for diagnostic and curative surgery. While a considerable proportion of such cases receives a pathological diagnosis of lung malignancy, it is imperative to consider alternative benign conditions in the differential diagnosis, such as PAP-like changes.

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Introduction

A ground-glass opacity (GGO) is a radiological finding on high-resolution computed tomography (HRCT), manifesting as a nebulous opacity that does not obscure the underlying bronchial structures or pulmonary vessels (Hansell et al. 2008). A ground-glass nodule (GGN), which progressively expands, closely resembles well differentiated lung adenocarcinoma (LUAD) and preinvasive lesions such as adenocarcinoma in situ (AIS) (Miller et al. 1981, Lee et al. 2014). The curative efficacy of surgery for AIS approaches 100%, and has a low perioperative rate of complications (Wang et al. 2019; Yotsukura et al. 2021). Consequently, surgical intervention is considered when the lesion gradually enlarges or a solid component becomes apparent on imaging performed during monitoring.

GGOs can also manifest as a wide variety of benign conditions (Miura et al. 2013). Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by excessive accumulation of phospholipids and surfactant apoproteins in distal air spaces. A hallmark feature of PAP on HRCT is the presence of smoothly thickened intralobular interstitial and septal lines, set against a background of widespread GGOs. This pattern is often referred to as 'crazy-paving' and is typically distributed in a bilateral and geographic manner (Khan and Agarwal 2011; Akira et al. 2016). On the other hand, some patients with fibrosis and chronic inflammation exhibit focal histological characteristics resembling PAP (Katzenstein 2016; Nunomura et al. 2016). Herein, we present an unusual case of a patient with pathologically confirmed focal PAP-like changes that were initially not suspicious, but then manifested as a progressively enlarging pure GGN mimicking AIS.

Case Presentation

A 63-year-old man with a history of smoking and exposure to dust underwent a wedge resection of his right lower lobe for lung cancer. The histopathological evaluation of the surgical specimen revealed AIS. Postoperative follow-up CT examinations four years after surgery revealed a pure GGN in the right upper pulmonary lobe, which gradually increased in size over the course of two years. At the time of evaluation for his GGN, the patient was asymptomatic, and his physical examination was unremarkable. Chest radiography and pulmonary and cardiac function tests, and blood tests that included levels of lactate

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Correspondence: Kazuki Hayasaka, Department of Thoracic Surgery, Aomori Prefectural Central Hospital, 2-1-1 Higashi Tsukurimichi, Aomori, Aomori 030-8553, Japan.
e-mail: kzk55hysk@gmail.com

dehydrogenase (LDH), Krebs von den Lungen-6 (KL-6), and pulmonary surfactant protein-D (SP-D), yielded unremarkable results. HRCT of the chest showed a pure GGN enlarging to 1.6 cm in the right pulmonary apex (Fig. 1A, B). The patient was clinically diagnosed with AIS and underwent wedge resection.

The surgical specimen was negative for malignant findings, whereas it contained airspaces filled with granular proteinaceous exudate that was positive on periodic acid-Schiff (PAS) staining and immunohistochemical staining for surfactant protein A (SP-A) (Fig. 2A-D). Foamy macrophages were also present in the airspaces. The stroma was mildly infiltrated by lymphocytes and macrophages (Fig. 2B). These pathological features were similar to those of PAP, except for their distribution and focal and localized manifestations, which deviated from the typical presentation of PAP. Measurement of the serum concentration of antibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) could not be performed. We ultimately concluded that the available evidence provided limited support for a diagnosis of PAP, leading to the diagnosis of PAP-like pathological changes in this particular patient. Fifteen months after his surgery, the patient appeared stable, without further progression of the condition.

Discussion

The findings in this case highlight the histopathological PAP-like changes that were initially unsuspected and ultimately manifested as a progressively enlarging pure GGN clinically mimicking AIS. A crazy-paving pattern with a bilateral and geographic distribution is the primary HRCT feature that is generally considered to be diagnostic of PAP (Khan and Agarwal 2011; Akira et al. 2016). Granular proteinaceous materials that are positive for PAS and SP-A staining within the alveolar spaces are the histopathological characteristics of PAP (Khan and Agarwal 2011). The diagnosis of autoimmune PAP, which encompasses over 90% of all PAP cases, relies predominantly on laboratory testing for antibodies to GM-CSF (Khan and Agarwal 2011). In our patient, the histopathological findings indicated PAP; however, a definitive diagnosis of PAP could not be established because the lesion was focal and localized and we could not obtain data on GM-CSF testing. Secondary PAP is recognized to emanate from underlying conditions such as hematopoietic and immunodeficiency disorders, dust inhalation, or infection. However, such etiological factors were not applicable to this case.

Throughout the six-year follow-up period subsequent to the initial surgical intervention for lung cancer, there were no appearances of typical GGOs indicative of PAP, except for enlargement of the pure GGN in the right upper lobe. The patient remained asymptomatic, and blood testing, including LDH, KL-6, and SP-D levels, yielded unremarkable results. These clinical findings further support that this is an atypical case of PAP. However, we acknowledge that the absence of data on the serum concentration of antibodies to GM-CSF is a problematic limitation, and it cannot be definitively discounted that our patient may have true autoimmune PAP.

There has been a published report of a patient whose initial imaging results showed a part-solid nodule, and follow-up imaging showed progression to a “crazy paving” pattern. That report supports the plausibility that a GGN can be an early radiological manifestation of PAP (Oh et al. 2014) Therefore, we plan to continue careful observation of our patient.

Some patients with fibrosis and chronic inflammation occasionally exhibit focal histopathological features resembling PAP (Katzenstein 2016; Nunomura et al. 2016). Shinohara et al. (2018) reported a patient with a 12-millimeter nodular GGO on CT, along with histopathological evidence consistent with the characteristics of PAP in the background of inflammation and fibrosis. Focal PAP-like lesions occurring in the background of other inflammatory

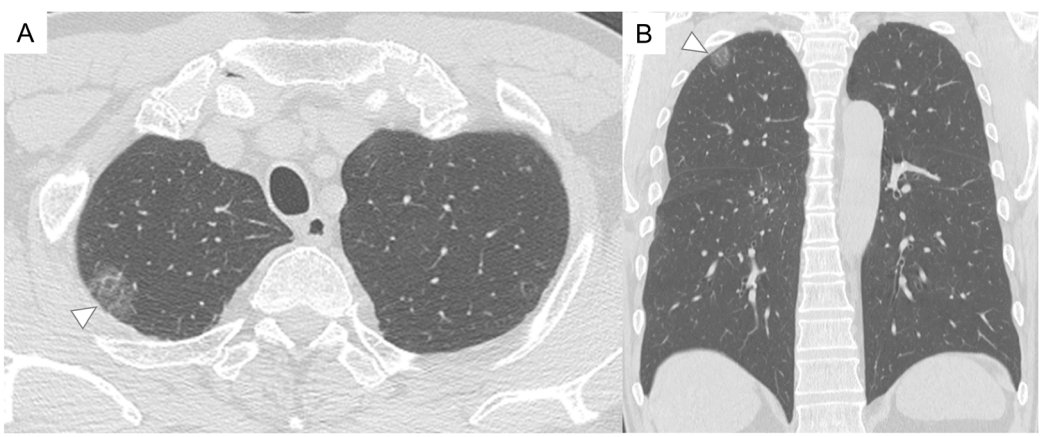

Fig. 1. Computed tomography (CT) findings.
High-resolution CT of the chest revealed a pure ground-glass nodule in the right pulmonary apex, which was enlarged, measuring 1.6 cm in the axial (A) and coronal planes (B) (arrowhead). No CT characteristics conventionally associated with PAP were evident, aside from the postoperative changes observed in the right lower lobe.

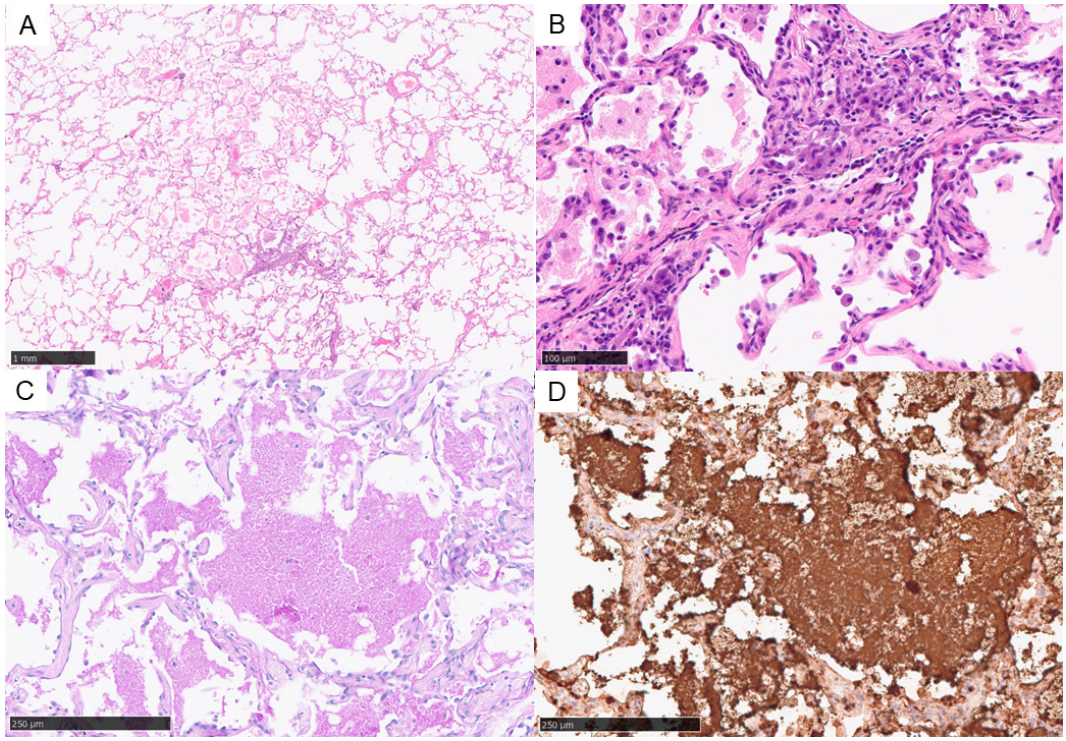

Fig. 2. Pathological findings.
Histopathological examination revealed that the airspaces were filled with granular proteinaceous exudates (hematoxylin and eosin stain) (A). Mild infiltration of lymphocytes and macrophages was seen in the stroma around a small vessel. Airspaces contained foamy macrophages (B). The granular proteinaceous substances present in the alveolar space were positive for periodic acid-Schiff staining (C) and surfactant protein A immunohistochemical staining (D).

and fibrotic diseases most likely represent nonspecific reactive changes, and such cases should not be diagnosed as PAP (Katzenstein 2016). PAP-like findings are caused by an imbalance between surfactant production by the alveolar epithelium and its subsequent degradation and absorption by macrophages and lymphatic vessels. Our present case was unique, given the absence of pathological conditions typically associated with PAP-like lesions, although the definitive etiology underlying the emergence of PAP-like changes has remained elusive.

With regard to the radiographical features of our case, a retrospective review on the CT findings revealed that a pure GGN can manifest as a "miniature crazy paving pattern"; wherein the ground-glass shadow reflects the accumulation of proteinaceous materials in the alveoli and the vascular shadows within the GGN reflect thickened alveolar septa. We also found a slightly reduced density of the nodule in our patient, and the nodule manifested a pattern with more mottling than seen for the patterns in most patients with AIS.

The Guidelines for the Management of Pulmonary Nodules in Japan recommend a workup to establish a definitive diagnosis for patients in whom the maximal diameter of a pure GGN enlarges to 15 mm or more (Japanese Society for CT Screening 2013). A major proportion of surgically confirmed single pure GGNs have been identified as preinvasive lesions such as AIS or minimally invasive adenocarcinoma (MIA); although GGNs may also manifest as benign nodules, including focal interstitial fibrosis, inflammatory granuloma, and inflammatory pulmonary pseudotumors (Wang et al. 2019). Given the low perioperative complication rate and an almost 100% surgical cure rate observed in patients with AIS or MIA (Wang et al. 2019, Yotsukura et al. 2021), we contend that pursuing a definitive diagnosis through surgery in our case was a judicious course of action. A pitfall of this case was that the differential diagnosis only included well differentiated LUAD, MIA, or AIS; and PAP was not suspected. In addition, in our daily practice, we found that patients with GGNs often present with multiple synchronous or metachronous GGNs, which can lead to misdiagnosis.

Conclusions

We have reported an unusual case presenting as PAP-like pathological features, which initially eluded suspicion and then presented as a progressively enlarging pure GGN clinically mimicking AIS. Patients who are being monitored for a pure GGN that enlarges over time should be considered for surgical intervention, which can provide both a diagnosis and a cure. While a substantial number of such cases are pathologically diagnosed with well differentiated LUAD, it is imperative to consider alternative benign conditions such as PAP-like changes in the differential diagnosis.

References

Akira, M., Inoue, Y., Arai, T., Sugimoto, C., Tokura, S., Nakata, K., Kitaichi, M. & Osaka Respiratory Diseases Symposia Group (2016) Pulmonary Fibrosis on High-Resolution CT of Patients With Pulmonary Alveolar Proteinosis. *AJR Am. J. Roentgenol.*, **207**, 544-551.

Hansell, D.M., Bankier, A.A., MacMahon, H., McLoud, T.C., Muller, N.L. & Remy, J. (2008) Fleischner Society: glossary of terms for thoracic imaging. *Radiology*, **246**, 697-722.

Japanese Society for CT Screening (2013) Japanese Society for CT Screening Guidelines for the management of pulmonary nodules detected by low-dose CT lung cancer screening version 3. https://www.jscts.org/pdf/guideline/gls3rd_english130621.pdf [*Accessed:* February 3, 2024].

Katzenstein, A.L. (2016) *Diagnostic Atlas of Non-Neoplastic Lung Disease: A Practical Guide for Surgical Pathologists*, 1st ed., Springer Publishing Company, Danvers, MA, pp. 112.

Khan, A. & Agarwal, R. (2011) Pulmonary alveolar proteinosis. *Respir. Care*, **56**, 1016-1028.

Lee, H.Y., Choi, Y.L., Lee, K.S., Han, J., Zo, J.I., Shim, Y.M. & Moon, J.W. (2014) Pure ground-glass opacity neoplastic lung nodules: histopathology, imaging, and management. *AJR Am. J. Roentgenol.*, **202**, W224-233.

Miller, P.A., Ravin, C.E., Smith, G.J. & Osborne, D.R. (1981) Pulmonary alveolar proteinosis with interstitial involvement. *AJR Am. J. Roentgenol.*, **137**, 1069-1071.

Miura, A., Akagi, S., Nakamura, K., Ohta-Ogo, K., Hashimoto, K., Nagase, S., Kohno, K., Kusano, K., Ogawa, A., Matsubara, H., Toyooka, S., Oto, T., Ohtsuka, A., Ohe, T. & Ito, H. (2013) Different sizes of centrilobular ground-glass opacities in chest high-resolution computed tomography of patients with pulmonary veno-occlusive disease and patients with pulmonary capillary hemangiomatosis. *Cardiovasc. Pathol.*, **22**, 287-293.

Nunomura, S., Tanaka, T., Nakayama, T., Otani, K., Ishii, H., Tabata, K., Kondoh, Y., Kataoka, K., Johkoh, T., Taniguchi, H. & Fukuoka, J. (2016) Pulmonary alveolar proteinosis-like change: A fairly common reaction associated with the severity of idiopathic pulmonary fibrosis. *Respir. Investig.*, **54**, 272-279.

Oh, S.J., Choo, J.Y., Lee, K.Y., Kim, J.H. & Yeom, S.K. (2014) Localized pulmonary alveolar proteinosis: two case reports. *Balkan Med. J.*, **31**, 257-260.

Shinohara, T., Hino, H., Imanishi, S., Naruse, K., Ohtsuki, Y. & Ogushi, F. (2018) Atypical pulmonary alveolar proteinosis presenting as a mixed nodular ground-glass opacity with focal mucinosis mimicking lung cancer. *J. Thorac. Dis.*, **10**, E694-E698.

Wang, J., Ma, H., Ni, C.J., He, J.K., Ma, H.T. & Ge, J.F. (2019) Clinical characteristics and prognosis of ground-glass opacity nodules in young patients. *J. Thorac. Dis.*, **11**, 557-563.

Yotsukura, M., Asamura, H., Motoi, N., Kashima, J., Yoshida, Y., Nakagawa, K., Shiraishi, K., Kohno, T., Yatabe, Y. & Watanabe, S.I. (2021) Long-Term Prognosis of Patients With Resected Adenocarcinoma In Situ and Minimally Invasive Adenocarcinoma of the Lung. *J. Thorac. Oncol.*, **16**, 1312-1320.