Received: 26 May 2023 | Accepted: 31 July 2023

DOI: 10.1002/rcr2.1204

CASE REPORT

Respirology Case Reports OPEN ACCESS APSR WILEY

Metachronous bilateral immunoglobulin G4-related pleuritis: A case report and literature review

Keitaro Tanabe[1] | **Takahiro Homma**[1,2,3] | **Shoko Matsui**[4] | **Tomoshi Tsuchiya**[1] | **Hisashi Saji**[3]

[1]Division of Thoracic Surgery, University of Toyama, Toyama, Japan

[2]Division of Thoracic Surgery, Kurobe City Hospital, Kurobe, Japan

[3]Department of Chest Surgery, St. Marianna University School of Medicine, Kawasaki, Japan

[4]First Department of Internal Medicine, University of Toyama, Toyama, Japan

Correspondence
Takahiro Homma, Department of Chest Surgery, St. Marianna University School of Medicine, 2-16-1 Sugao, Kawasaki, Kanagawa 216-8511 Japan.
Email: takahiro.homma@marianna-u.ac.jp

Funding information
The Ministry of Health, Labor and Welfare Research Program on Rare and Intractable Diseases, Grant/Award Number: JPMH20FC1040; The Japan Society for the Promotion of Science, Grant/Award Number: 19K08645

Associate Editor: Coenraad F Koegelenberg

Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized disease, and therefore its clinical features are not yet fully understood. Here, we describe a surgical case of metachronous bilateral IgG4-related pleuritis and postoperative chylothorax. This case could provide key insights into the pathology of IgG4-RD from a surgical perspective. We present a 70-year-old woman who had a right pleural mass. Video-assisted thoracoscopic pleural mass resection was performed, and the patient was diagnosed with right-sided IgG4-related pleuritis. Two years later, she was also diagnosed with left-sided IgG4-related pleuritis. We suspected the presence of IgG4-positive plasma cell infiltration. Additionally, she experienced a complicated postoperative chylothorax on the left side. It is important to consider the altered course of lymphatic vessels when extensively removing the pleura near the right thoracic duct. The occurrence of metachronous bilateral IgG4-associated pleuritis has not been previously reported, making this case particularly significant for understanding the pathology of IgG4-RD from a surgical standpoint.

KEYWORDS
chylothorax, IgG4-related disease, pleural mass, pleuritis

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a systemic, chronic, and inflammatory disorder characterized by the enlargement of involved organs, elevated immunoglobulin (Ig)-G4 levels, and abundant infiltration of plasmacytes with IgG4 and fibrosis in involved organs.[1] IgG4-RD has become gradually recognized; however, there remain unresolved aspects concerning its aetiology, pathogenesis, early diagnosis, and natural course.

Here, we describe a case of metachronous bilateral IgG4-related pleuritis. We suspected IgG4-positive plasma cell infiltration from the right to left side, based on both the imaging and pathological findings. The patient also had a complicated postoperative chylothorax on the left side. Although IgG4-RD is systemic, no metachronous bilateral IgG4-associated pleuritis has surprisingly been reported; thus, this case could be key to understanding the pathology of IgG4-RD from a surgical viewpoint. We also review previous reports on the cause of metachronous bilateral pleuritis and postoperative chylothorax.

CASE REPORT

A 72-year-old woman was referred to our hospital with complaints of right back pain. Her medical history included osteoporosis and lumbar canal stenosis. Chest computed tomography (CT) revealed a mass lesion, measuring 67 × 18 mm, on the right chest wall without pleural effusion (Figure 1A). The mass was accompanied by high uptake on positron emission tomography (PET) (Figure 1B). Video-assisted thoracoscopic pleural mass

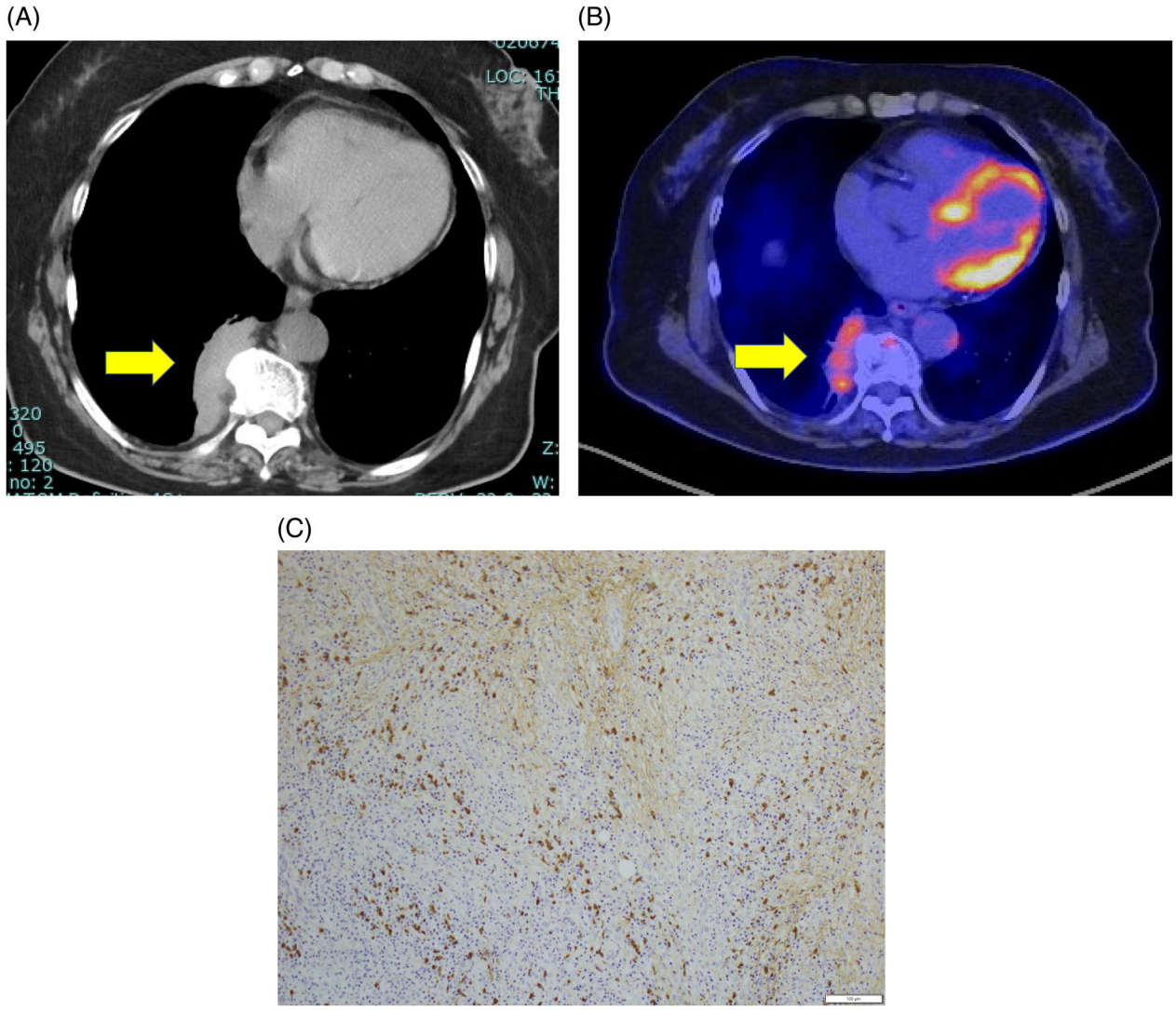

FIGURE 1 (A) Computed tomography showing a right pleural mass (arrow) without pleural effusion. (B) Positron emission tomography showing uptake of the right pleural mass (arrow). (C) Pathologic examination of the right pleura showing numerous immunoglobulin (Ig)-G and IgG4-positive plasma cells (IgG4 immunostaining, original magnification ×100).

resection was performed in September 2019 to rule out malignancy. The mass pleura was slightly reddish, thickened, and very hard with vague borders, unlike the normal pleura. The mass was strongly adhered to the bony thorax. The pathological diagnosis of IgG4-related pleuritis was made (Figure 1C). Her serum IgG4 level was within the normal range, but a pleural specimen showed a dense lymphocytic infiltrate with a ratio of IgG4-positive plasma cells to total plasma cells of >50% and 100 IgG4-positive plasma cells per high-power field with storiform fibrosis, confirming IgG4-RD. There were no IgG4-related lesions in other organs. Subsequently, she was followed up regularly at our outpatient clinic, without additional treatment.

Two years later, a growing pleural mass was found in the left chest wall, measuring 26 × 12 mm, and PET showed a high accumulation of the mass (Figure 2A, B). Although the imaging findings were similar to those of the right side 2 years prior, we judged that surgical resection was needed to rule out malignant disease. Video-assisted thoracoscopic surgical mass resection was performed in October 2021 (Figure 2C). There were tight adhesions between the mass and bony thorax. The pathological diagnosis was IgG4-RD, as before (Figure 2D), and her postoperative course was uncomplicated. However, during the postoperative 3 weeks, she was admitted to the clinic with dyspnea, and a massive left pleural effusion was found (Figure 3A). The pleural fluid had a milky white appearance, and the triglyceride level in the pleural fluid was 1388 mg/dL (>110 mg/dL). Based on the findings of the cytological analysis of fluid stained with Sudan III, she was diagnosed with chylothorax and treated with continuous drainage of pleural fluid and a low-fat diet. For both diagnosis and treatment, lymphangiography was

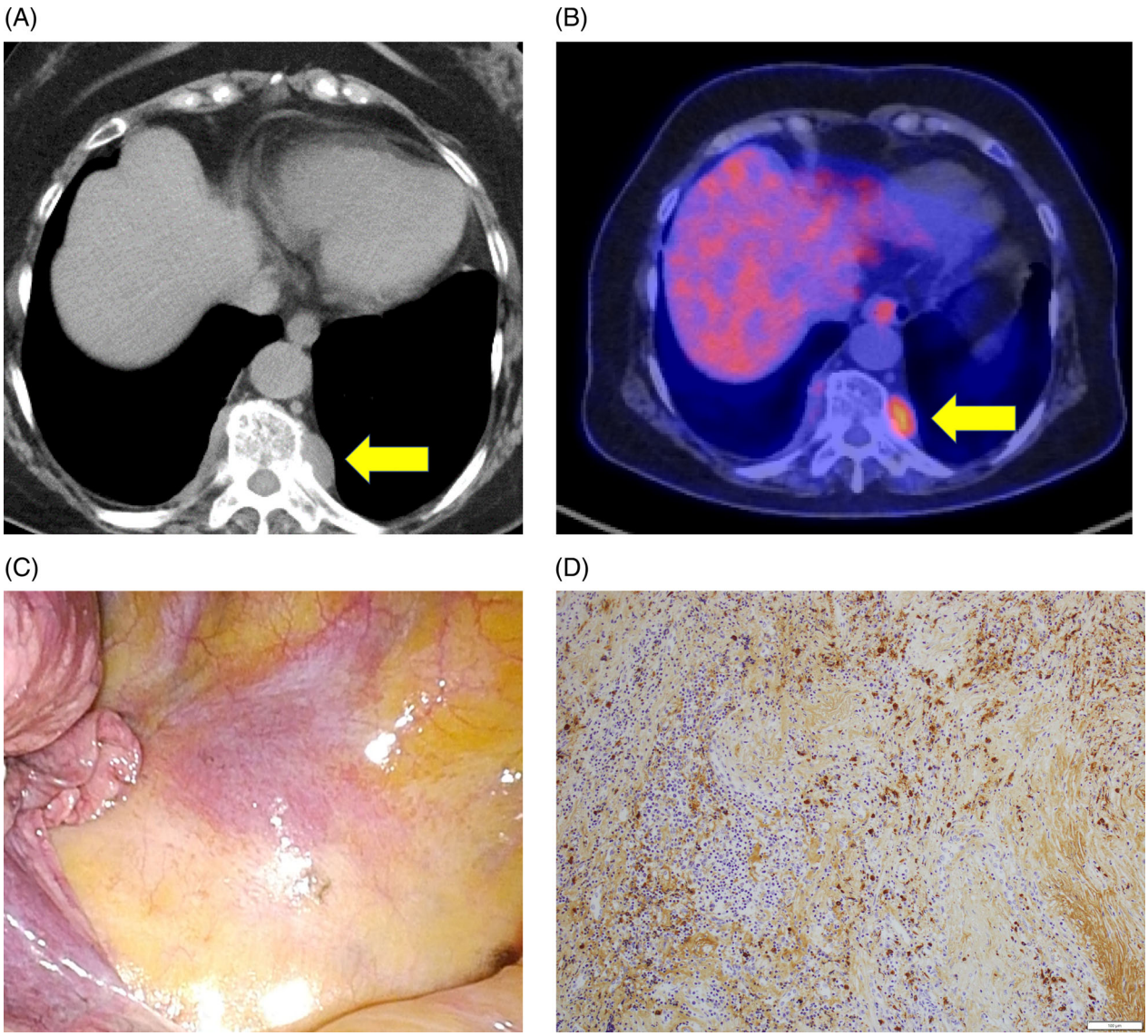

FIGURE 2 (A) Computed tomography showing a left pleural mass (arrow) without pleural effusion. There is no obvious right pleural mass recurrence. (B) Positron emission tomography showing uptake of the left pleural mass (arrow). There is no obvious uptake in the postoperative right pleural thickness. (C) Intraoperative thoracoscopic finding showing a reddish, thickened pleural mass unlike the normal pleura. The border is vague. (D) Pathologic examination of the left pleura showing numerous immunoglobulin (Ig)-G and IgG4-positive plasma cells (IgG4 immunostaining, original magnification ×100).

performed 7 days after the start of drainage. The findings showed that thoracic lymphatic vessels flowed predominantly on the left side, with few on the resected right side. No leakage of the lymphangiographic agent into the left thoracic cavity confirmed that the thoracic duct injury was in the healing stage (Figure 3A). A chest CT scan after lymphangiography showed pooling of the lymphangiographic agent around the resected left pleura (Figure 3B). The pleural effusion gradually decreased after lymphangiography. The thoracic drain was removed on day 11 after the drainage began, and the patient was discharged on day 14. The patient has had no recurrence since discharge from the hospital without additional treatment.

DISCUSSION

IgG4-RD is a systemic fibro-inflammatory disease characterized by elevated serum IgG4 levels and distinctive histopathological findings, such as lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis.[1] Although almost all organs in the body can be affected by IgG4-RD, pleural involvement is observed in only 4% of cases.[2,3] Seventy-five percent of reported cases of IgG4-related pleuritis were found to have pleural effusions.[4] A definitive diagnosis of IgG4-RD cannot be obtained by examination of pleural effusion, and patients with IgG4-related pleuritis tend to have higher adenosine deaminase even though they do not have tuberculosis.[5]

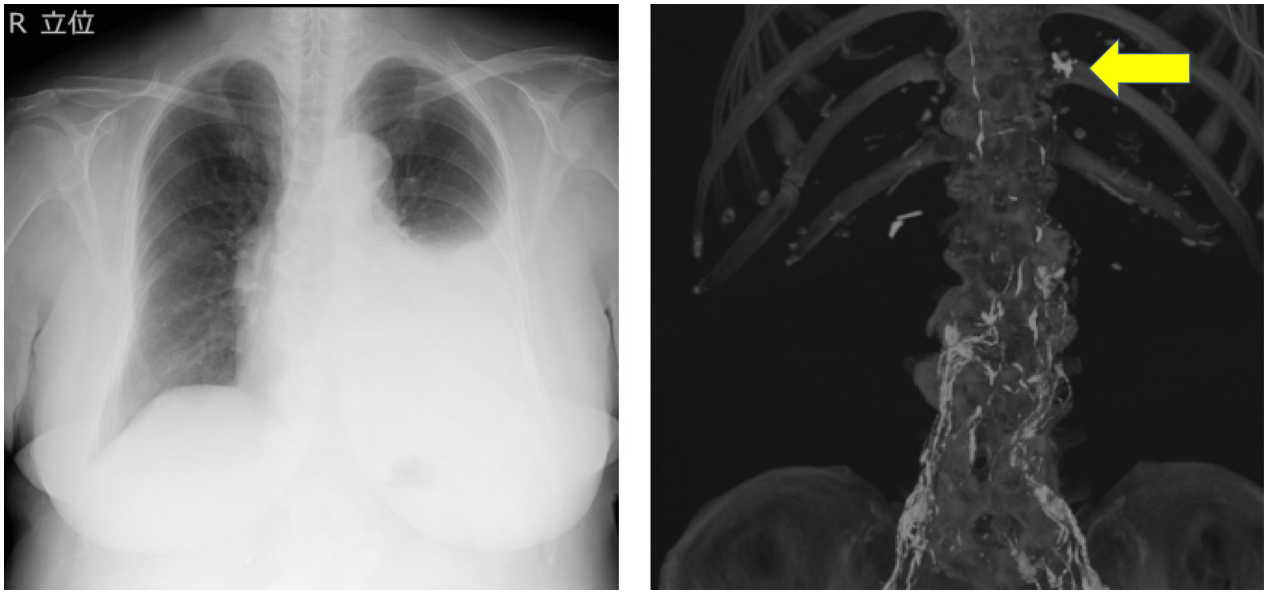

FIGURE 3 (A) Postoperative chest x-ray showing pleural effusion on the left side. (B) Lymphangiography showing no leakage into the left thoracic cavity.

Although there are reports of thickened pleura,[4,6] pleural tumours are rare. Malignancies were observed in 10.4% of patients with IgG4-RD.[7,8] PET cannot distinguish between IgG4-RD and malignant tumours, because IgG4-RD also often shows PET accumulation.[9–14] Besides, there was a patient with the destruction of thoracic vertebrae-like malignant tumours even with IgG4-RD.[15] Therefore, surgical biopsy is required to differentiate IgG4-RD from malignant tumours. Metachronous pathology is a characteristic phenomenon that may occur in multiple organs in patients with IgG4-RD. Bilateral IgG4-associated pleuritis has been reported in 8 cases,[16–23] and metachronous IgG4-related pleuritis has not been reported.

Respiratory involvement in IgG4-RD occurs via the lymphatic route. Intrathoracic lesions can be found in the mediastinum, lungs, and pleurae. The American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD are reported to be very good in both sensitivity and specificity for differentiating IgG4-RD from similar systemic diseases, such as Sjögren syndrome and anti-neutrophil cytoplasmic antibody-associated vasculitis.[24] According to the classification criteria, paravertebral band-like soft tissue in the thorax in the Th8–11 paravertebral column of the chest is described as a highly specific finding. However, these components have not been fully elucidated. The thoracic duct arising from the cisterna chyli at T12–L2 typically runs cranially along the right midline and then enters the left side at the level of the third thoracic vertebra, although there are many variations in the thoracic duct.[25] We resected a wider pleural area, including the mass near the thoracic duct. Therefore, the lymphatic route may occlude the right main pathway and change it to the left. This case showed two things: (1) paravertebral band-like soft tissue was fibrous tissue involving the lymphatic vessels; and (2) the lymphatic pathway was changed from the right to the left, which was considered to cause IgG4-positive plasma cell infiltration along lymphatic vessels and metachronous bilateral IgG4-related disease.

To the best of our knowledge, this is the first case of metachronous bilateral IgG4-related pleuritis without pleural effusion. The patient had complicated postoperative chylothorax on the left side. Previous right resection was thought to alter lymphatic pathways, causing IgG4-positive plasma cell infiltration into the contralateral pleura, metachronous bilateral onset, and postoperative chylothorax.

This case was rare case due to several aspects, including (1) there are no previous reports of metachronous bilateral IgG4-related pleuritis; (2) almost every reported patient with IgG4-related pleuritis report had pleural effusion, and IgG4-related pleuritis is rarely discovered as a mass; (3) the clinical course of contralateral recurrence after pleural mass resection was suspected with IgG4-positive plasma cell infiltration through lymph flow; (4) wide pleurectomy around the right thoracic duct causes altered lymphatic pathways and association with contralateral postoperative chylothorax; and (5) previous reports were only of biopsy cases, as there have been no reports of extensive pleural resection. Thus, the present case serves to offer a lesson from a surgical viewpoint.

There are some reports of IgG4-related pleuritis, but bilateral IgG4-pleuritis is very rare. To investigate this in detail, a literature search of the PubMed database was conducted in January 2023 (Table 1). The search used the following terms ‘IgG4’, ‘related’, ‘pleuritis’, ‘bilateral’ and ‘metachronous’. Papers published until the date of review that contained these terms in the title or abstract were selected. The reference lists of the identified papers and

TABLE 1 Reported cases of bilateral IgG4-pleuritis.

Case	Author	Age	Sex	Chief complaints	Chief features	Onset	Other Ig4-RD	PET	Surgical procedure	Thoracoscopic findings	Postoperative complications	Treatment	Initial dose of prednisolone
1	Yasokawa et al.[16]	46	M	Dyspnea	Pleural effusion	Synchronous	None	No accumulation	Biopsy	Numerous small, blister-like nodules	None	Prednisolone	30 mg/day
2	Yamamoto et al.[17]	78	M	General fatigue, fever	Pleural effusion	Synchronous	None	No accumulation	Biopsy	NA	None	Diuretics	None
3	Sakata et al.[18]	66	M	Edema	Pleural effusion	Synchronous	None	NA	Biopsy	Normal	None	Prednisolone → Rituximab (combination use)	70 mg (1 mg/kg/day)
4	Nagayasu et al.[19]	81	M	Dyspnea	Pleural effusion	Synchronous	None	NA	Biopsy	NA	None	Prednisolone	30 mg/day (0.6 mg/kg/day)
5	Mizushina et al.[20]	70	F	Cough	Pleural effusion	Synchronous	None	NA	Biopsy	Normal	None	Prednisolone	30 mg/day
6	Ishida et al.[21]	74	F	Dyspnea, edema	Pleural effusion	Synchronous	None	NA	Biopsy	Thickness, reddish	Pleural effusion	Prednisolone	25 mg/day (0.5 mg/kg/day)
7	Kato et al.[22]	69	M	Cough, dyspnea	Pleural effusion	Synchronous	Lung	Uptake	Biopsy	Thickness	None	Prednisolone	30 mg/day
8	Kita et al.[23]	65	M	Cough, dyspnea	Pleural effusion	Metachronous	Lung	Uptake in the lung	Biopsy	Thickness	None	Observation → Prednisolone	30 mg/day
9	Present case	72	F	Back pain	Pleural mass	Metachronous	None	Uptake	Pleural resection	Thickness, reddish	Chylothorax	Observation	None

relevant manuscripts were examined. Titles and abstract information were selected based on subject importance. Studies that were not definitively excluded based on abstract information were also selected for full-text screening. The full text of all relevant researchers was examined to evaluate the possibility of inclusion. The exclusion criteria were as follows: (1) studies that did not focus on the topic selected, (2) papers in a language other than English, (3) duplicates, and (4) studies not available from libraries for full-text assessment. Publications indexed as articles, proceedings papers, or reviews were reviewed, including the references of the publications to identify additional relevant articles and a total of 28 papers were included in the review.

The present case also provides some lessons from a surgical viewpoint. The risk of postoperative chylothorax should be carefully considered, assuming disruption to the lymphatic pathway. IgG4-related pleural thoracoscopic findings varied from normal[17,19,26] to abnormal, which were expressed as numerous small, white, and dense granular lesions and reddish, hyperemia, and blister-like nodules.[9,10,15,21,22,27] This case showed a reddish, thickened pleura, which differs from the findings of most previous reports. Accumulation of pleural findings may provide new information for the diagnosis of IgG4-RD. Steroid use may prevent or reduce left IgG4-associated pleuritis. However, the attending physician was reluctant to use steroids because of concerns about worsening osteoporosis.

We described a case of metachronous bilateral IgG4-associated pleuritis. The patient had complicated postoperative chylothorax following a left pleural tumour lesion. We postulated that previous right resection disrupted the lymphatic pathways, causing contralateral infiltration to the thorax, metachronous bilateral onset, and postoperative chylothorax.

AUTHOR CONTRIBUTIONS

Conceptualization: Keitaro Tanabe and Shoko Matsui. *Methodology, software, validation, formal analysis, investigation, data curation, writing—review and editing, visualization, and project administration*: Takahiro Homma. *Administrative support*: Takahiro Homma, Shoko Matsui, Tomoshi Tsuchiya and Hisashi Saji. *Writing—original draft preparation and funding acquisition*: Shoko Matsui. *Provision of study materials or patients*: Keitaro Tanabe and Takahiro Homma. *Final approval of manuscript*: All authors.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.com) for English language editing.

This case was presented as an abstract at the 39th Annual Meeting of the Japanese Association for Chest Surgery, Tokyo, 2022.

FUNDING INFORMATION

This study was supported by the Ministry of Health, Labor and Welfare Research Program on Rare and Intractable Diseases (No. JPMH20FC1040) and the Japan Society for the Promotion of Science (No. 19K08645).

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

ORCID

Takahiro Homma https://orcid.org/0000-0001-5117-5570

REFERENCES

1. Wallace ZS, Naden RP, Chari S, Choi HK, Della-Torre E, Dicaire JF, et al. The 2019 American College of Rheumatology/European league against rheumatism classification criteria for IgG4-related disease. Ann Rheum Dis. 2020;79:77–87. https://doi.org/10.1136/annrheumdis-2019-216561
2. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol. 2010;34:1812–9. https://doi.org/10.1097/PAS.0b013e3181f7266b
3. Breant J, Fleury MF, Delque G, Vascaut L. Effect of guided ventilation on gas exchange in kypho-scoliotic patients in post-intensive care. Rev Pneumol Clin. 1989;45:206–14.
4. Kasashima S, Kawashima A, Ozaki S, Kita T, Araya T, Ohta Y, et al. Clinicopathological features of immunoglobulin G4-related pleural lesions and diagnostic utility of pleural effusion cytology. Cytopathology. 2019;30:285–94. https://doi.org/10.1111/cyt.12641
5. Shimoda M, Tanaka Y, Morimoto K, Okumura M, Shimoda K, Takemura T, et al. IgG4-related pleural effusion with high adenosine deaminase levels: a case report and literature review. Medicine (Baltimore). 2021;100:e25162. https://doi.org/10.1097/MD.0000000000025162
6. Saito Z, Yoshida M, Kojima A, Tamura K, Kuwano K. Characteristics of pleural effusion in IgG4-related pleuritis. Respir Med Case Rep. 2020;29:101019. https://doi.org/10.1016/j.rmcr.2020.101019
7. Yamamoto M, Takahashi H, Tabeya T, Suzuki C, Naishiro Y, Ishigami K, et al. Risk of malignancies in IgG4-related disease. Mod Rheumatol. 2012;22:414–8. https://doi.org/10.1007/s10165-011-0520-x
8. Ishizuka K, Shikino K, Yokokawa D, Ikusaka M. Follicular lymphoma with hepatic accumulation on FDG-PET/CT masquerading IgG4-related disease. Radiol Case Rep. 2021;16:2886–9. https://doi.org/10.1016/j.radcr.2021.07.008
9. Tamura K, Suzuki M, Ishii S, Takasaki J, Naka G, Iikura M, et al. IgG4-related disease with elevated adenosine deaminase in pleural effusion diagnosed clinically using thoracoscopy under local anesthesia and FDG-PET-CT. Respir Med Case Rep. 2020;30:101066. https://doi.org/10.1016/j.rmcr.2020.101066
10. Makimoto G, Ohashi K, Taniguchi K, Soh J, Taniguchi A, Miyahara N, et al. Long-term spontaneous remission with active surveillance in IgG4-related pleuritis: a case report and literature review. Respir Med Case Rep. 2019;28:100938. https://doi.org/10.1016/j.rmcr.2019.100938
11. Kondo T, Uehara T. Immunoglobulin G4-related disease with fibroinflammatory lesions in the pleura, bile ducts and pericardium. CMAJ. 2016;188:188972. https://doi.org/10.1503/cmaj.160186
12. Ishikawa H, Uruga H, Fujii T, Kurosaki A, Morokawa N, Takaya H. IgG4-related disease in the differential diagnosis of lung nodules. Respirol Case Rep. 2020;8:e00550. https://doi.org/10.1002/rcr2.550
13. Gajewska ME, Rychwicka-Kielek BA, Sørensen K, Kubik M, Hilberg O, Bendstrup E. Immunoglobulin G4-related pleuritis: a case report. Respir Med Case Rep. 2016;19:18–20. https://doi.org/10.1016/j.rmcr.2016.05.006
14. Doita S, Tamura T, Baba T, Oomori H, Nishii K, Nakanishi M, et al. A case of immunoglobulin G4-related disease with pleural effusion, requiring exclusion of tuberculous pleurisy. Respir Med Case Rep. 2022;37:101654. https://doi.org/10.1016/j.rmcr.2022.101654
15. Rumalla K, Smith KA, Arnold PM. Immunoglobulin G4-related epidural inflammatory pseudotumor presenting with pulmonary complications and spinal cord compression: case report. J Neurosurg Spine. 2017;26:688–93. https://doi.org/10.3171/2016.11.SPINE16924
16. Yasokawa N, Shirai R, Tanaka H, Kurose K, Oga T, Oka M. Thoracoscopic findings in IgG4-related pleuritis. Intern Med. 2020;59:257–60. https://doi.org/10.2169/internalmedicine.3031-19
17. Yamamoto H, Suzuki T, Yasuo M, Kobayashi O, Tsushima K, Ito M, et al. IgG4-related pleural disease diagnosed by a re-evaluation of chronic bilateral pleuritis in a patient who experienced occasional acute left bacterial pleuritis. Intern Med. 2011;50:893–7. https://doi.org/10.2169/internalmedicine.50.4726
18. Sakata K, Kikuchi J, Emoto K, Kotaki T, Ota Y, Nishina N, et al. Refractory IgG4-related pleural disease with Chylothorax: a case report and literature review. Intern Med. 2021;60:2135–43. https://doi.org/10.2169/internalmedicine.6313-20
19. Nagayasu A, Kubo S, Nakano K, Nakayamada S, Iwata S, Miyagawa I, et al. IgG4-related pleuritis with elevated adenosine deaminase in pleural effusion. Intern Med. 2018;57:2251–7. https://doi.org/10.2169/internalmedicine.0387-17
20. Mizushina Y, Shiihara J, Nomura M, Ohta H, Ohyanagi F, Morishita Y, et al. Immunoglobulin G4-related pleuritis complicated with minimal change disease. Intern Med. 2022;61:723–8. https://doi.org/10.2169/internalmedicine.7010-20
21. Ishida A, Furuya N, Nishisaka T, Mineshita M, Miyazawa T. IgG4-related pleural disease presenting as a massive bilateral effusion. J Bronchology Interv Pulmonol. 2014;21:237–41. https://doi.org/10.1097/LBR.0000000000000082
22. Kato E, Takayanagi N, Ishiguro T, Kagiyama N, Shimizu Y, Sugita Y. IgG4-related pleuritis with chylothorax. Intern Med. 2014;53:1545–8. https://doi.org/10.2169/internalmedicine.53.1642
23. Kita T, Araya T, Ichikawa Y, Terada N, Kawashima A, Kasashima S, et al. IgG4-related pleuritis with No other organ involvement. Am J Med Sci. 2018;356:487–91. https://doi.org/10.1016/j.amjms.2018.05.004
24. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25:1181–92. https://doi.org/10.1038/modpathol.2012.72
25. Johnson OW, Chick JF, Chauhan NR, Fairchild AH, Fan CM, Stecker MS, et al. The thoracic duct: clinical importance, anatomic variation, imaging, and embolization. Eur Radiol. 2016;26:2482–93. https://doi.org/10.1007/s00330-015-4112-6
26. Shimada H, Kato Y, Okuda M, Fukuda K, Tanaka M, Okuda Y, et al. Pleuritis associated with immunoglobulin G4-related disease under normal thoracoscopic findings: a case report. J Med Case Reports. 2021;15:241. https://doi.org/10.1186/s13256-021-02718-4
27. Mei F F, Mancini M, Maurizi G, Vecchione A, Zuccatosta L, Rendina EA, et al. Pleural involvement in IgG4-related disease: case report and review of the literature. Diagnostics (Basel). 2021;11:2177. https://doi.org/10.3390/diagnostics11122177

How to cite this article: Tanabe K, Homma T, Matsui S, Tsuchiya T, Saji H. Metachronous bilateral immunoglobulin G4-related pleuritis: A case report and literature review. Respirology Case Reports. 2023; 11:e01204. https://doi.org/10.1002/rcr2.1204