CASE REPORT

IgG4-related mastitis, a rare disease, can radiologically and histologically mimic malignancy

Rin Yamada,¹ Shin-ichiro Horiguchi,¹ Toshinari Yamashita,² Terumi Kamisawa³¹Department of Pathology, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Tokyo, Japan²Department of Breast Surgery, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Tokyo, Japan³Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Tokyo, Japan**Correspondence to**
Dr Rin Yamada,
r.yamada82@gmail.com

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SUMMARY

IgG4-related disease (IgG4-RD) is characterised by high serum concentrations of IgG4, dense lymphoplasmacytic infiltrates, storiform fibrosis and increased IgG4-positive plasma cells in tissues. This systemic disease occurs in various organs metachronously, but IgG4-related mastitis appears extremely rare. We report a case of IgG4-related mastitis, radiologically considered to represent breast cancer mainly composed of intraductal component and requiring histological differentiation from mucosa-associated lymphoid tissue (MALT) lymphoma. The breast mass disappeared with steroid therapy. When patients have a breast mass, regardless of the presence or absence of IgG4-RD, IgG4-related mastitis should be considered in addition to breast cancer. If histological findings show dense lymphoplasmacytic infiltrates, IgG4-related mastitis should be suspected in addition to malignant lymphoma, and lack of monoclonality should be confirmed. To avoid unnecessary surgery or chemotherapy, knowledge and accurate diagnosis of the entity of IgG4-related mastitis is necessary.

BACKGROUND

IgG4-related disease (IgG4-RD) is a recently proposed entity characterised by high serum concentrations of IgG4, dense lymphoplasmacytic infiltrates, storiform fibrosis and increased IgG4-positive plasma cells in tissues.^{1–3} This systemic disease occurs in various organs either synchronously or metachronously.^{1–3–8} However, IgG4-related mastitis is extremely rare.^{9–11} We report a case of IgG4-related mastitis mimicking malignancy radiologically and histologically.

CASE PRESENTATION

A 71-year-old woman had been diagnosed with IgG4-related dacryoadenitis 4 months earlier. She also had a history of diabetes, cataract and osteoporosis. A left breast mass was identified on contrast-enhanced CT performed as screening for IgG4-RD. This mass was palpable, painless and elastic hard.

INVESTIGATIONS

Serum IgG level was elevated (2761 mg/dL; normal range, 870–1700 mg/dL). Serum IgG4 level was markedly elevated, at 1430 mg/dL (upper limit of normal: 135 mg/dL). An enhanced, 12 mm mass was noted in the upper outer quadrant of the left breast on contrast-enhanced CT ([figure 1](#)). Mammography and ultrasonography showed an indistinct mass. MRI with gadolinium enhancement revealed an irregularly bordered mass with early

Figure 1 Contrast-enhanced CT of the breast. An enhanced, 12 mm mass is apparent in the upper outer quadrant of the left breast.

enhancement, around which linear and dot-like enhancements were observed ([figure 2](#)).

DIFFERENTIAL DIAGNOSIS

Radiologically, breast cancer mainly comprising intraductal component was considered.

TREATMENT

Mammotome biopsy was performed for definitive diagnosis.

OUTCOME AND FOLLOW-UP

Microscopic examination revealed scattered terminal ductal-lobular units with dense lymphoplasmacytic infiltration ([figure 3A](#)). Mammary glands were markedly atrophied. Lymphoplasmacytes surrounded ducts and formed lymphoid follicles with lymphocytic infiltration into ductal epithelia similar to

Figure 2 MRI with gadolinium enhancement of the breast. An irregularly bordered mass with early enhancement is seen, around which linear and dot-like enhancements are observed.

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Figure 3 (A–D) Pathological findings from mammotome biopsy. (A) Dense lymphoplasmacytic infiltration with lymphoid follicles and markedly atrophic mammary glands. (B) Lymphoplasmacytes have infiltrated into ductal epithelia, similar to LEL. (C) Stromal fibrosis with focal hyalinisation is seen. (D) Most plasmacytes show positive immunohistochemical reactions for IgG4. LEL, lymphoepithelial lesion.

lymphoepithelial lesions (LELs; [figure 3B](#)). Lymphoplasmacytes also extended to adipose tissue around mammary parenchyma. Most lymphocytes within lymphoid follicles were CD20-positive B cells, and scattered CD3-positive T cells were seen around lymphoid follicles. In some parts, stromal fibrosis with focal hyalinisation was seen ([figure 3C](#)). Obliterative phlebitis was not evident. Cellular atypia was not evident in the lymphocytes, plasma cells, stromal cells or epithelia. Owing to LELs, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with plasmacytoid differentiation was

considered. However, immunoglobulin light-chain restriction was not seen on immunohistochemistry, and no immunoglobulin heavy chain rearrangement was detected by Southern blot analysis ([figure 4](#)). MALT lymphoma was therefore considered unlikely. Most plasmacytes showed positive immunohistochemical reactions for IgG and IgG4 ([figure 3D](#)). The number of IgG4-positive plasma cells was 162/high-power field (HPF) and the ratio of IgG4/IgG-positive cells was 76%. The final diagnosis was IgG4-related mastitis. One month later, multiple nodules appeared in the subcutaneous tissue of the patient's forearm, and were histopathologically diagnosed as IgG4-related skin disease. Since the breast mass was not critical and the patient had diabetes, cataract and osteoporosis, she was followed-up without steroid therapy. However, 11 months later, she reported difficulty moving her eyes due to swelling of the eyelids. Oral prednisolone was started at 22.5 mg/day (0.4 mg/kg) for 4 weeks. The dose was subsequently tapered to 5 mg/day over 11 months. Eyelid swelling promptly disappeared. The breast mass and subcutaneous nodules disappeared at the same time and were not palpable at 3 months after starting prednisolone. No recurrences occurred under maintenance therapy with low-dose prednisolone (5 mg/day) during the year after starting treatment.

Figure 4 Southern blot analysis. Immunoglobulin heavy chain rearrangement is not detected.

DISCUSSION

IgG4-RD was first proposed by Kamisawa *et al.*¹² in 2003, in a study of autoimmune pancreatitis (AIP) in which serum IgG4 level was increased and IgG4-positive plasma cell infiltration was seen. IgG4-positive plasma cell infiltration has also been observed in patients with other conditions, including

Table 1 Clinicopathological features

Case number	Sex/ age	Breast lesion		IgG4 test (mg/dL)	IgG4+/IgG+plasm cells/HPF	Obliterative phlebitis	Lesion other than breast	Treatment	Outcome
		Number of lesion	Laterality						
1 ⁹	F/46	1	Left	185		+	—	—	No recurrence at 1 year
2 ¹⁰	F/48	6	Right	350	272/421 (65%)	—	—	—	No recurrence at 1 year
3 ¹⁰	F/51	3	Left		405/479 (85%)	—	Eyelid swelling	—	No recurrence at 3 years
4 ¹⁰	F/37	2	Right		383/467 (82%)	—	Lymphadenopathy	—	No recurrence at 6 years
5 ¹⁰	F/54	1	Right		495/1005 (49%)	+	—	—	No recurrence at 11 years
6 ¹¹	F/51	1	Right	217		—	—	Steroid therapy	No recurrence at 7 months
Present case	F/71	1	Left	1430	162/213 (76%)	—	Dacryoadenitis, Skin disease	Steroid therapy	No recurrence at 1 year

retroperitoneal and mediastinal fibrosis, inflammatory pseudotumour of the lung and liver, Küttner tumour and interstitial nephritis, all of which are now referred to as IgG4-RDs.^{1 3–8} Comprehensive diagnostic criteria for IgG4-RD were proposed in Japan in 2012, involving: (1) characteristic diffuse/localised swelling or masses in single or multiple organs; (2) elevated serum IgG4 concentrations (≥ 135 mg/dL); and (3) marked lymphocyte and plasmacyte infiltration, fibrosis and infiltration of IgG4-positive plasma cells, defined as a ratio of IgG4/IgG-positive cells $>40\%$ and >10 IgG4-positive plasma cells per HPF.² International histological consensus criteria were also proposed in 2012, to provide practising pathologists with a set of guidelines for the diagnosis of IgG4-RD, resting on the combined presence of the characteristic histopathological appearance and increased numbers of IgG4-positive plasma cells.¹³ The critical histopathological features were: (1) dense lymphoplasmacytic infiltrate; (2) fibrosis, usually storiform in character; and (3) obliterative phlebitis. Moreover, minimal criteria were recommended to consider previously unrecognised organs or sites being involved with IgG4-RD, as: (1) characteristic histopathological findings with elevated numbers of IgG4-positive plasma cells and ratios of IgG4/IgG-positive cells; (2) high serum IgG4 concentrations; (3) effective response to steroid therapy; and (4) reports of other organ involvements consistent with IgG4-RD.

IgG4-related mastitis is extremely rare. To the best of our knowledge, only six cases have been reported in the English literature (table 1).^{9–11}

These were diagnosed as ‘inflammatory pseudotumour’, ‘IgG4-related sclerosing mastitis’ or ‘IgG4-related sclerosing disease of the breast’. Recently, nomenclatures describing individual organ manifestations of IgG4-RD have been preferred. In the breast, the term ‘IgG4-related mastitis’ was recommended.¹⁴ The patients ranged in age from 37 to 71 years (mean, 51 years). All patients were female. One case involved multiple bilateral lesions, but the others had one or two unilateral lesions. In four tested patients, serum IgG4 levels were elevated. Three cases showed lesions in areas other than the breast, such as eyelid swelling, lymphadenopathy, dacryoadenitis and skin disease. Histological findings of IgG4-related mastitis resembled IgG4-RD in other organs, such as dense lymphoplasmacytic infiltrates, storiform fibrosis and increased tissue IgG4-positive plasma cells. In only two cases, obliterative phlebitis was seen.

In two cases, steroid therapy was added. No recurrence has been reported in any cases, with follow-ups ranging from 7 months to 11 years. Only the present case and one in the literature fulfilled the comprehensive diagnostic criteria for IgG4-RD, because information on serum IgG4 concentrations and the ratio of IgG4/IgG-positive cells were not available in the other cases. All cases fulfilled the international histological consensus criteria, although obliterative phlebitis was seen in only two cases. Since only a few cases were reported as IgG4-related mastitis, the minimal criteria needed to be applied. All cases showed the characteristic histopathological appearance. However, information on serum IgG4 concentrations and the ratio of IgG4/IgG-positive cells was available in only two cases, as mentioned above. Only the present case confirmed both effective response to steroid therapy and the presence of IgG4-RD in other organs, in addition. The skin lesion in this case also fulfils minimal criteria.

This case mimicked malignancy both radiologically and histologically. First, we considered a breast cancer mainly comprising of an intraductal component, because of the radiological findings of an irregularly bordered mass with early enhancement, around which were seen linear and dot-like enhancements. In two cases, breast cancer could not be ruled out radiologically. AIP often mimics pancreatic cancer on radiological imaging, leading to unnecessary surgery.^{15 16} It is the same for other IgG4-RDs.^{3 17} When patients show a breast mass with IgG4-RD in other organs, we need to consider IgG4-related mastitis in addition to breast cancer. However, more than half of the cases (4 of 7) showed no IgG4-RD in other organs, and we do not generally measure serum IgG4 concentrations. Even if patients do not show IgG4-RD in other organs, we need to consider IgG4-related mastitis.

Second, histological findings such as dense lymphoplasmacytic infiltration and LEL mimic MALT lymphoma with plasmacytoid differentiation as the second most common form of malignant lymphoma of the breast next to diffuse large B-cell lymphoma.¹⁸ In two cases, the possibility of malignant lymphoma was seriously considered initially. In other organs, the difficulty in differentiating IgG4-RD from malignant lymphoma including MALT lymphoma was also indicated.^{19 20} Moreover, MALT lymphoma arising from a background of IgG4-related chronic inflammation and IgG4-positive MALT lymphoma were

reported in salivary glands, ocular adnexa, lymph nodes, meningeal dura and thyroid, although the pathogenetic role of IgG4 expression is unclear at present.^{21–28} We cannot make a diagnosis of IgG4-RD based solely on IgG4-positive lymphoplasmacytic infiltration. Yamamoto *et al*²⁹ reported that malignancies including MALT lymphoma occurred in 10.4% of patients with IgG4-RD (11 of 106), representing a higher proportion than that for the general population. Cheuk *et al*²⁵ also showed that ocular adnexal lymphoma occurred in 10% of patients with IgG4-RD (3 of 30), all of which were MALT lymphoma except for 1 follicular lymphoma. Owing to the histological similarity of IgG4-RD to MALT lymphoma and the increasing risk of malignancy, it is important to confirm a lack of monoclonality by immunoglobulin light-chain restriction and Southern blot analysis, in addition to IgG and IgG4 immunostaining to exclude malignant lymphoma.

Steroid therapy is effective for IgG4-RD. In two cases, IgG4-related mastitis was successfully treated in this manner. Since all patients with IgG4-related mastitis were well with no recurrence after biopsy and IgG4-related mastitis is not critical, steroid therapy would demand a degree of IgG4-RD in other organs and consideration of the side effects of steroid therapy.

In conclusion, we report a case of IgG4-related mastitis mimicking malignancy radiologically and histologically. When patients have a breast mass, regardless of the presence or absence of IgG4-RD, we need to consider IgG4-related mastitis in addition to breast cancer. If histological findings show dense lymphoplasmacytic infiltrates, we should suspect IgG4-related mastitis in addition to malignant lymphoma and confirm a lack of monoclonality. To avoid unnecessary operations or chemotherapy, it is important to recognise the entity of IgG4-related mastitis and make an accurate diagnosis.

Learning points

- IgG4-related mastitis is an extremely rare disease that can mimic malignancy radiologically and histologically.
- When patients have a breast mass, regardless of the presence or absence of IgG4-RD, we need to consider IgG4-related mastitis in addition to breast cancer.
- If histological findings show dense lymphoplasmacytic infiltrates, we should suspect IgG4-related mastitis in addition to malignant lymphoma and confirm a lack of monoclonality.
- Steroid therapy is effective against IgG4-related mastitis as IgG4-RD in other organs.

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Patient consent Obtained.

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