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https://doi.org/10.15017/4479049

出版情報：福岡醫學雜誌. 112 (1), pp.51-58, 2021-03-25. Fukuoka Medical Association
バージョン：
権利関係：

Case Report

Possible Case of IgG4-related Mastitis : A Case Report and Review of the Literature

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Abstract

IgG4-related disease (IgG4-RD) has been recognized as a distinct disease entity, and the occurrence of IgG4-RD in the breast, is extremely rare. In this report, we describe a possible case of IgG4-related mastitis.

A 55-year-old Japanese female presented with a left breast tumor. Ultrasound examination demonstrated a hypoechoic tumor in the left upper outer quadrant and lymph node swelling. The tumor had become larger, and a right breast tumor was also noted. Accordingly, surgical resection of the left breast tumor was performed. After the surgery, parotid gland tumors and multiple lung nodules were noted, and the serum IgG4 level was elevated (144 mg/dL). A histopathological study demonstrated dense lymphoplasmacytic infiltration with lymphoid follicle formation, fibrosclerosis and obliterative phlebitis. Immunohistochemical analyses revealed substantial IgG4-positive plasma cell infiltration ; however, the IgG4/IgG-positive plasma cell ratio was 23.6%. Accordingly, this patient was considered to have a possible case of IgG4-related mastitis.

Additional studies are needed to clarify the clinicopathological features of IgG4-related mastitis because the diagnostic criteria for this disease have not yet been established.

Key words : IgG4-related mastitis, IgG4-positive plasma cells, mastitis.

Introduction

IgG4-related disease (IgG4-RD) has been recognized as a distinct clinicopathological disease entity and is considered a multiorgan immune-mediated condition. This disease is characterized clinically by the formation of tumor-like lesions and elevated serum IgG4 concentrations and histopathologically by the presence of fibrosclerosis, dense lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells and a high IgG4/IgG-positive plasma cell ratio accompanied by eosinophilic infiltration and obliterative phlebitis. The common sites of involvement are the pancreas (autoimmune pancreatitis), salivary and lacrimal glands (Mikulicz's disease), and retroperitoneum (retroperitoneal fibrosis). Additionally, IgG4-RD can involve various organs, such as the orbits, nasal cavity, meninges, lymph nodes, thyroid glands, lungs, aorta, kidneys, liver, and skin[1)~11)]. Different symptoms appear depending on the site of the lesion, sometimes with serious complications. For example, obstruction due to swelling and thickening of organs and organ dysfunction associated with fibrosis can occur. The occurrence of IgG4-RD in the breast is

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extremely rare ; only 16 such cases have been reported in the English literature[12)~23)]. In the present report, we describe a possible case of IgG4-related mastitis and discuss the clinicopathological features of the disease.

Case presentation

A 55-year-old Japanese female was referred to our hospital with a left breast tumor. Physical examination revealed a relatively well-circumscribed tumorous lesion, measuring 5 cm in diameter, in the left upper outer quadrant. On mammography, localized asymmetrical nodular lesions were noted in the left breast (Fig. 1A). Ultrasound demonstrated many hypoechoic lesions (maximum diameter 57.0 mm) with internal hyperechoic foci and swelling of the bilateral axillary lymph nodes (maximum diameter 13.8 mm), which lacked the hilum structure (Fig. 1B). Then, biopsy of the left axillary lymph node was performed due to a clinical diagnosis of malignant lymphoma. Because we could not obtain a definitive diagnosis from the results, a subsequent biopsy of the left breast was performed. Based on a result of plasma cell mastitis, the patient underwent follow-up mammography and ultrasound. However, she noticed a contralateral breast lump, during the follow-up period, which appeared as two localized asymmetrical nodular lesions on mammography 20 months after the first visit to the hospital (Fig. 1C). The ultrasound finding was similar to that of the left breast tumors, which was larger (diameter approximately 20 mm) than the previous tumor (Fig. 1D). The ultrasound findings of the left breast tumor were not changed (Fig. 1E). Based on the tumor enlargement and the patient's decision, surgical resection of the left breast tumor was performed under general anesthesia.

Histopathological examination of the resected left breast tumor demonstrated a relatively well-circumscribed tumor (Fig. 2A) composed of a dense infiltration of lymphocytes and plasma cells with accompanying fibrosclerosis (Fig. 2B). Many lymphoid follicle formations with reactive germinal centers were noted, and dense plasma cell infiltration was mainly observed around the lymphoid follicles. These lymphocytes appeared mature and small in size, and plasma cells also showed no atypia (Fig. 2C). Obliterative phlebitis was noted (Fig. 2F, 2G), and eosinophilic infiltration was also observed. Neither epithelioid granuloma nor neutrophilic infiltration was noted. Immunohistochemical analyses revealed substantial IgG4-positive plasma cell infiltration (56/high-power field) (Fig. 2D) ; however, the IgG4/IgG-positive plasma cell ratio was 23.6% (Fig. 2E). *In situ* hybridization analyses revealed no monoclonal plasma cell proliferation because kappa- and lambda-positive plasma cells were evenly distributed. After the surgery, the patient noted swelling of the right parotid gland, and multiple lung nodules were detected by imaging examinations. We performed cytologic examinations to rule out other diseases by aspiration and bronchoscopy for the parotid gland and lung nodules, respectively, both of which specimens had no specific findings. Base on those results, we considered IgG4-RD was the primary differential diagnosis for those lesions. We performed ultrasound of the parotid gland and computed tomography of the lung every six months. The imaging findings did not show significant changes over time. To confirm the diagnosis of IgG4-RD, we performed additional blood tests and found an elevated IgG4 level (144 mg/dL). No tumor recurrence was noted in the left breast at 66 months after the surgery, and no additional therapy, such as corticosteroids was performed.

Discussion

IgG4-RD is a rare autoimmune disease of unknown cause. The clinicopathological findings are fibrotic, mass-like, and hypertrophic lesions in organs throughout the body with lymphoproliferation[24)]. To date, only 16 cases of IgG4-related mastitis have been reported in the English literature[12)~23)]. Table 1 summarizes the clinico-

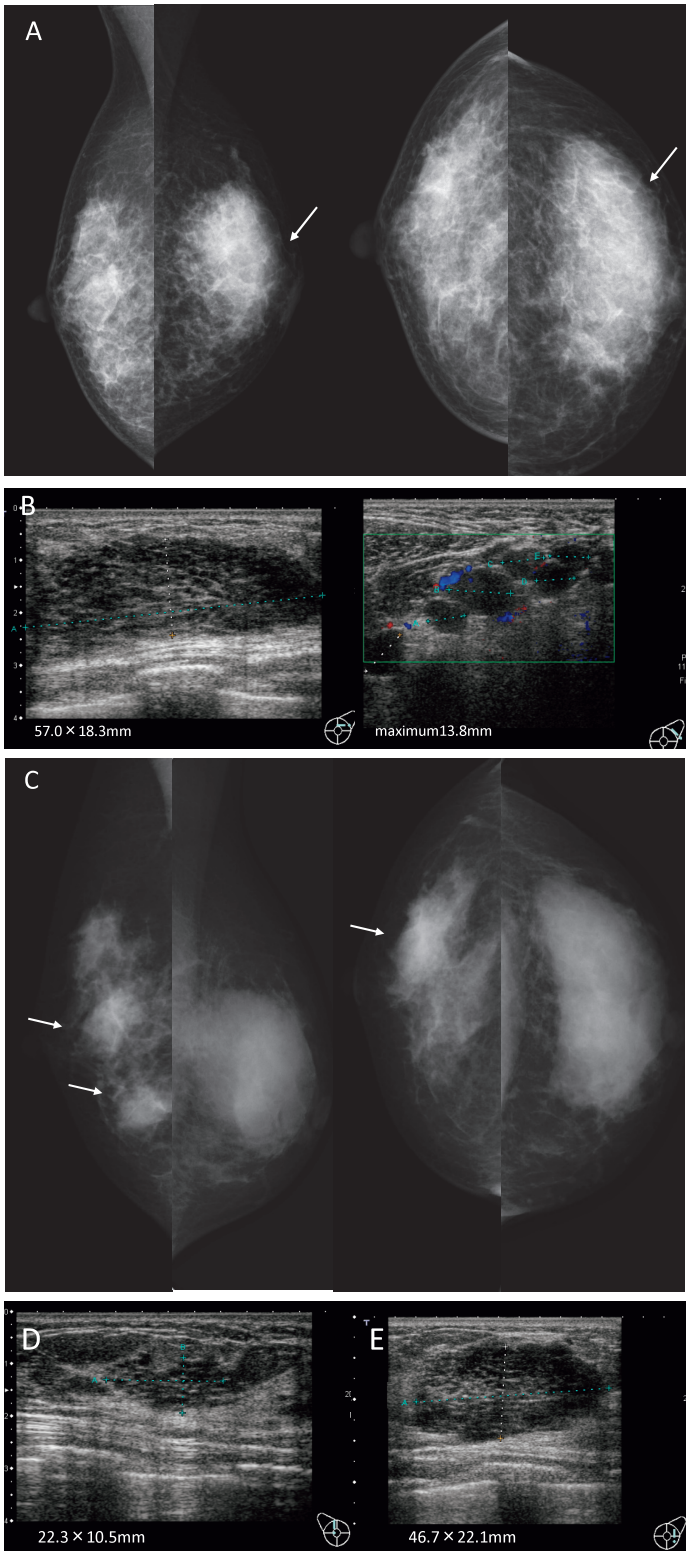

Fig. 1 Imaging examinations (**A**) Mammography at first visit. (**B**) Ultrasound at first visit. (diameter of left breast tumor 57.0 × 18.3mm, maximum diameter of left axillary lymph nodes 13.8mm) (**C**) Mammography during follow-up. (**D**) Ultrasound of right breast during follow-up. (diameter 22.3 × 10.5mm) (**E**) Ultrasound of left breast during follow-up. (diameter 46.7 × 22.1mm)

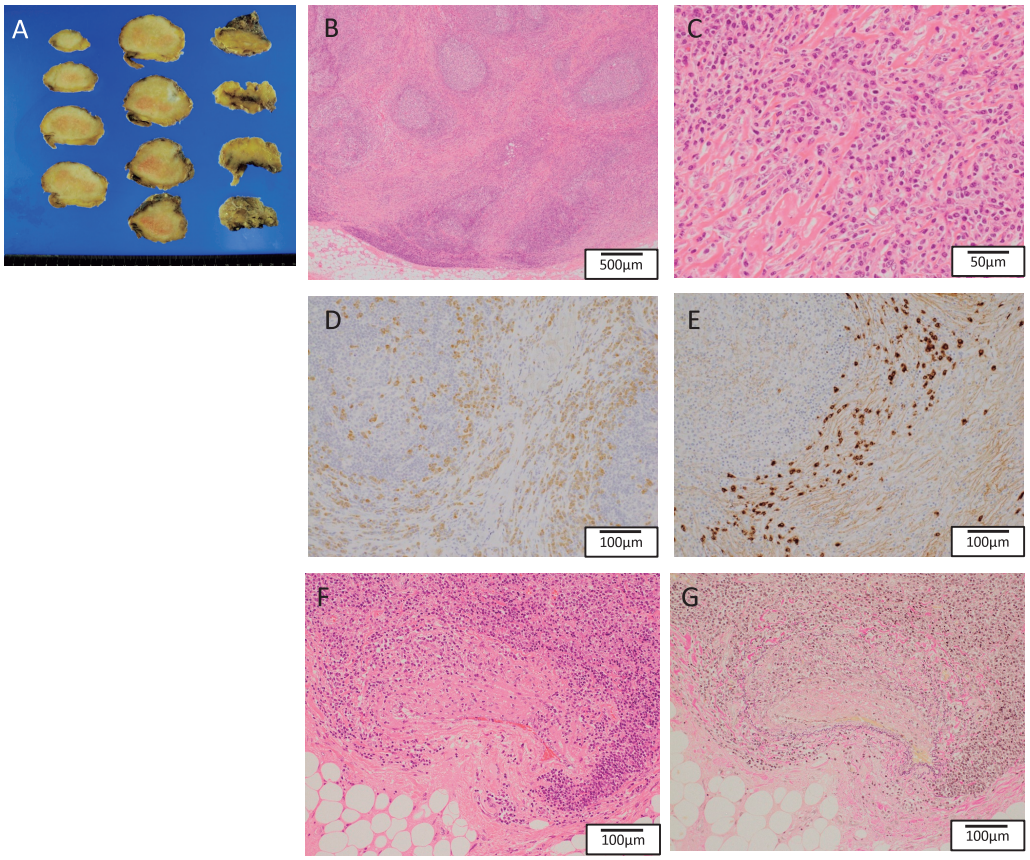

Fig. 2 Histopathological and immunohistochemical features of the left breast tumor.
(**A**) Resected tumor. (**B**) Dense lymphoplasmacytic infiltration with lymphoid follicles containing germinal centers (hematoxylin and eosin, × 40). (**C**) Abundant plasma cell infiltration without atypia and accompanying fibrosclerosis (hematoxylin and eosin, × 400). (**D**) Abundant IgG4-positive plasma cell infiltration was present (× 200). (**E**) IgG-positive plasma cells were present and were more than 4 times more abundant than IgG4-positive plasma cells (× 200). (**F**) Obliterative phlebitis (hematoxylin and eosin, × 200). (**G**) Obliterative phlebitis (elastica van gieson, × 200).

pathological features of those patients including the present case. The median age of those patients was 51 years (range 37–71) ; of those, one patient was male, and 15 were female[12)~23)]. Elevated serum IgG4 levels were noted in 9 of the 10 reported cases. IgG4-related mastitis with multiple organ involvement, such as the lymph nodes, pancreas, eyelids, and lacrimal and/or salivary glands was noted in 5 patients, while 11 patients had only breast lesions.

Here, we presented an additional possible case of IgG4-related mastitis. In this case, mammography showed localized asymmetrical nodular lesions, and the ultrasound findings showed multiple bilateral tumors and lymph nodes without the hilum structure. However, we cannot describe the characteristic image findings due to the small number of cases.

Regarding the comprehensive diagnostic criteria for IgG4-RD, Umehara *et al.* proposed the following :

i) diffuse/localized swelling or masses in single or multiple organs, ii) elevated serum IgG4 concentration (≥ 135 mg/dL), and iii) histopathologically, marked lymphocytes, plasma cell infiltration, fibrosis, and infiltration of IgG4-positive plasma cells in addition to an IgG4/IgG-positive plasma cell ratio > 40% and > 10 IgG4-positive plasma cells/high-power field [24)]. The diagnosis is definite when all three criteria are positive.

Table 1 Reported cases of IgG4-related mastitis

Case	Sex/Age	Symptoms	Lesion/ Laterality	Serum IgG4 (mg/dL)	Tissue IgG4/IgG plasma HPF	Extramanifestations	Diagnosis	Treatment	Outcomes
1	F/48	Painless palpable	Multiple bilateral	350	0.65	N/A	Excision	Excision	No recurrence at 1 y
2	F/51	Painless palpable	Multiple right	3900	0.85	Bilateral eyelid swelling	Excision	Excision	No recurrence at 3 y
3	F/37	Painless palpable	Multiple right	N/A	0.82	Diffuse lymphadenopathy (cervical, axillary, inguinal)	CNB	Observation	Resolution of beast lesion at 6 mo
4	F/54	Painless palpable	Single right	N/A	0.49	N/A	Excision	Excision	No recurrence at 11 y
5	F/46	Induration	Single right	185	N/A	N/A	Excision	Excision	No recurrence at 1 y
6	F/58	N/A	N/A	920	N/A	Mikulicz syndrome AIP	Excision	Excision, Steroid	No recurrence at 7 mo
7	F/51	Painless palpable	Single right	217	N/A	Bilateral eyelid swelling	CNB	Steroid	No recurrence at 7 mo
8	F/66	Painless palpable	Single left	N/A	0.639	N/A	Excision	N/A	N/A
9	F/71	Painless palpable	Single left	1430	0.76	Dacryoadenitis, Skin disease	Mammothome biopsy	Steroid	No recurrence at 1 y
10	F/45	Painless palpable	Single right	N/A	0.673	N/A	Excision	N/A	N/A
11	F/61	Painless nonpalpable	Single left	N/A	0.5	Chronic sialadenitis, nonalcoholic pancreatitis, Cervical mass	N/A	N/A	N/A
12	F/52	Asymptomatic	Single left	13.1	N/A	N/A	CNB	Excision	N/A
13	M/48	Palpable	Single right	N/A	0.51	N/A	CNB	Excision	N/A
14	F/43	Palpable	Single right	515	0.85	Bilateral lachrymal glands and submandibular glands, AIP, cervical mass	VACNB	Steroid	No recurrence at 2 mo
15	F/49	Painless palpable	Multiple left	1594	N/A	N/A	CNB	Steroid	N/A
16	F/70	Palpable(breast and axilla)	Multiple left	N/A	0.4≧	N/A	CNB	Steroid	No recurrence at 4 y

F, female ; M, male ; N/A, not available ; HPF, high-power field ; AIP, autoimmune pancreatitis ; CNB, core needle biopsy ; VACNB, vacuum-assisted core needle biopsy ; y, year ; mo, month

However, meeting the criteria of i) and iii) or i) and ii) indicates a probable or possible diagnosis, respectively[24]. In this case, we considered a differential diagnosis of other breast mastitis such as low-grade B-cell lymphoma, multicentric Castlman disease, and plasma cell mastitis. However, because the specific pathological findings were different from those of this case[25], we finally diagnosed a possible case of IgG4-RD. The present patient was a possible case based on the criteria of i) and ii). The criteria for iii) were not met because the IgG4/IgG-positive plasma cell ratio was less than 40%, although abundant IgG4-positive plasma cells were present within the lesion.

Administration of steroids might be effective for IgG4-RD depending on the patient's condition, but some reports have described relapse during steroid tapering[24]. Because IgG4-RD in the breast does not cause serious organ damage, we observed it and did not administer steroid treatment. However, follow-up is necessary because lesions in other organs can lead to serious pathological conditions.

Conclusion

We reported an additional case of IgG4-related mastitis. IgG4-RD should be considered the primary diagnosis if the clinicopathological findings show fibrotic, mass-like, and hypertrophic lesions in organs throughout the body with lymphoproliferation. IgG4-RD may lead to serious pathological conditions in other major organs, such as pancreatitis and nephritis. Steroid therapy is the first choice, but it is careful that some reports have described relapse during steroid tapering. Because the number of cases is small, further studies are needed to clarify the clinicopathological features and the diagnostic criteria.

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the patient.

Availability of data and materials

Not applicable

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Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

None of the authors received any funding.

Acknowledgements

We would like to thank AJE (www.aje.com) for English language editing.

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(Received for publication October 1, 2020)

（和文抄録）

IgG4 関連疾患疑診群の 1 例

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IgG4 関連疾患（IgG4-RD）は，一疾患として認識されており，乳腺における IgG4-RD は極めて珍しい．乳房における IgG4 関連疾患疑診群と診断した症例について報告する．症例は，55 歳の日本人女性で，左乳房腫瘤を自覚した．超音波検査では，左 C 区域の低エコーと両側の腋窩リンパ節腫大を示した．その後左乳房腫瘤の増大と右乳房腫瘍が指摘されたため，左乳房腫瘤に対して腫瘤摘出術が行われた．術後，耳下腺腫瘍と複数の肺結節が出現し，血清 IgG4 レベルが上昇していた（144mg/dL）．手術標本の病理結果は，リンパ濾胞周囲を主体に多数形質細胞が浸潤し，一部で線維化・硝子化を伴い静脈炎も観察された．免疫染色では，IgG4 陽性の形質細胞浸潤を認めたが，IgG4/IgG 陽性形質細胞比は 23.6%であったため，IgG4 関連疾患疑診群の診断となった．

この疾患の乳腺における診断基準がまだ確立されていないため，IgG4 関連乳腺炎の臨床病理学的特徴を明らかにするために症例の蓄積が必要である．

キーワード：IgG4 関連疾患，IgG4 陽性形質細胞，乳腺炎