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Immunoglobulin-G4 related mastitis: A case report☆

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ABSTRACT

INTRODUCTION: IgG4-related mastitis (IgG4-RM) is exceedingly rare with only ten cases reported in the literature to date. Organs that are affected with IgG4-related disease (IgG4-RD) all share the same histopathological hallmarks consisting of dense lymphocytic infiltration, storiform fibrosis and obliterative phlebitis.
PRESENTATION OF CASE: This case report highlights a case of IgG4-RM found incidentally in a 52-year-old woman during a routine breast screen and it explores the current literature about IgG4-RM and IgG4-RD.
DISCUSSION: IgG4-RM and IgG4-RD, in general, is a new entity in the field of medicine and its aetiology is not well understood. In the literature, IgG4-RM often presents as a painless palpable breast lump in isolation or with other systemic manifestations. IgG4-RM is considered benign and has excellent prognosis post-conservative treatment with steroid or surgical excision.
CONCLUSION: IgG4-RM is diagnosed exclusively on histological analysis. It is hard to distinguish IgG4-RD from malignant breast lesions purely on clinical examination and imaging studies. Increasing awareness of this condition among clinicians will assist them in managing patients better. Extensive whole body imaging is not recommended unless symptomatic.

1. Introduction

IgG4-related mastitis (IgG4-RM) is use to describe IgG4-related disease (IgG4-RD) of the breast [2]. It is clinically important because like all other IgG4-RD, it can mimic malignant conditions and can co-exist with other systemic manifestations [3]. We report a case of IgG4-RM in a patient undergoing screening mammography, treated in a specialised breast unit.

2. Presentation of case

Screening mammography is routinely offered to women from ages 50 to 70 in Australia nationwide. The patient is a previously well 52-year-old married woman who was attending her routine breast screen assessment and was recalled for a new lesion in the left breast.

She had no prior history of breast or ovarian cancers and was completely asymptomatic at the time of screening. Apart from Graves' disease and hypertension, she had no significant health issues. She had never smoked nor consumed alcohol and had not had exogenous hormonal therapy in the past. She had three adult children, only one who was breastfed for approximately six months. She is post-menopausal for the last two years at the time of assessment. Examination of the breast, axilla and neck were unremarkable.

Mammograms obtained from the screening are as depicted [see Fig. 1a and b]. The ultrasonographic views of the corresponding lesion of interest are shown as follows [see Fig. 1c]. As this lesion was new in comparison to imaging two years prior, an ultrasound-guided core biopsy of the lesion was performed.

Only three small fragmented linear tissues were available for analysis. This sample demonstrated scattered stromal cells with chronic inflammatory cells. Low-molecular cytokeratin (LMCK) stain for the specimen was negative, indicating that the specimen is likely benign. The result, however, was inconclusive as the sample size was small. Given the age of the patient and abnormal mammography findings, the patient elected to have an open biopsy with pre-operative hook-wire localisation for definitive diagnosis. Microphotographs of the open biopsy specimen are as shown [see Fig. 2a and b].

The lesion measures 7 mm in diameter and are well-circumscribed and tan in appearance. Microscopically, it is sparsely cellular with aggregates of lymphoid follicles and plasma cells that showed prominent expression of IgG4. Routine pathology tests indicate that her full blood count, serum creatinine and thyroid function tests were within normal limits. Serum immunology test-

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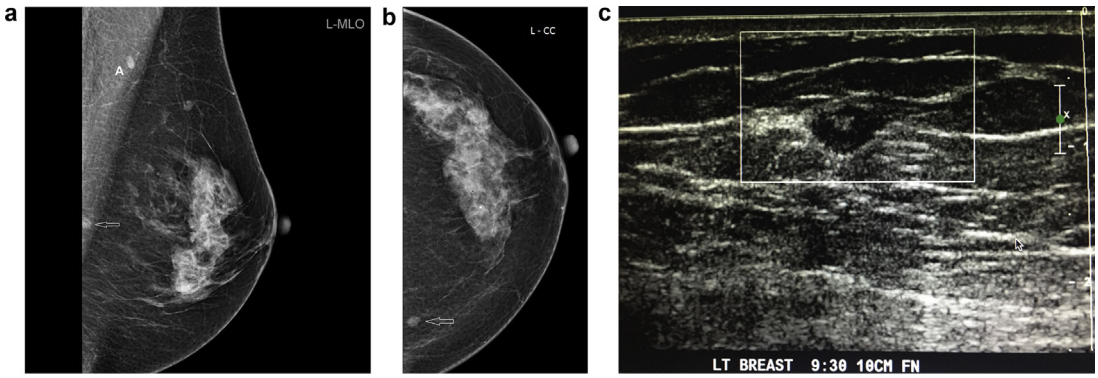

Fig. 1. Screening mammogram (a and b). (a) left breast – MLO. (b) left breast – CC. A new small circumscribed opacity is noted in the left breast at approximately 9 o'clock 10 cm from the nipple (arrows). Apart from a small normal appearing lymph node (marked A), no other new lesions were seen. [Reviewer Point 4]. (c) (Ultrasound) – A single targeted B-mode ultrasound image of the left breast with colour doppler assessment demonstrates a small solid avascular hypoechoic nodule with a tiny internal hyerechogenic foci. The lesion did not demonstrate any suspicious features, and correlates with the small circumscribed lesion noted on the mammography.

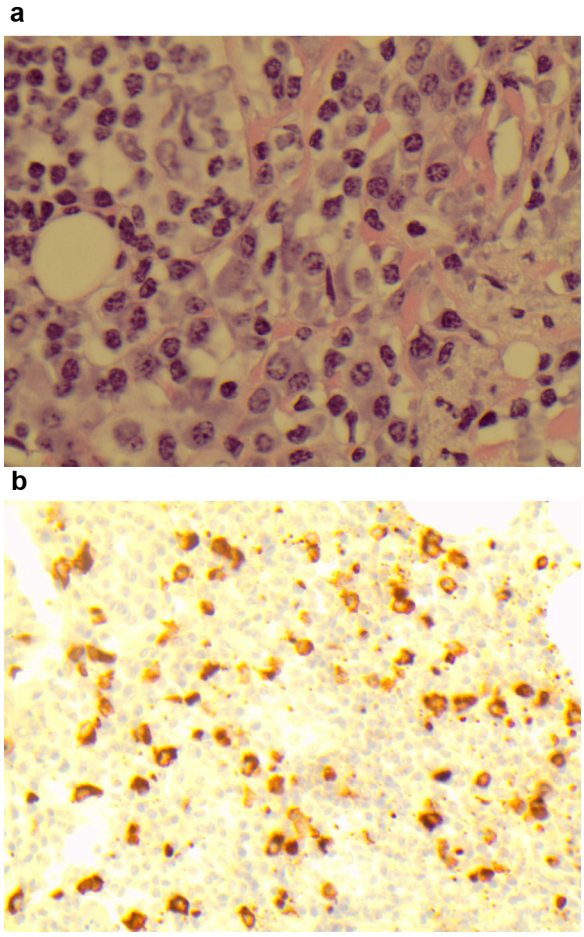

Fig. 2. (a) This micrograph is taken at 400× magnification and is stained with haemotoxylin and eosin. It shows a sparsely cellular specimen with aggregates of lymphoid follicles and plasma cells. (b) [Reviewer Point 7]. Immunohistohemical staining for IgG4 demonstrates prominent IgG4-positive plasma cell infiltrates in the specimen. [Reviewer Point 7].

ings showed normal levels of IgG4 but elevated total IgG level (Table 1).

The patient had an uneventful recovery from the procedure. As the patient had no other symptoms or signs to indicate extra-manifestations of IgG4-RD, no other imaging was performed.

Table 1
demonstrates the full panel of immunological tests performed.

Immunoglobulin levels	Levels (g/L)	Reference Range (g/L)
IgG	70.1	5.76–15.36
IgG1	12.4	4.05–10.11
IgG2	4.39	1.69–7.86
IgG3	0.95	0.11–0.85
IgG4	1.31	0.03–2.00
IgA	2.29	0.70–4.00
IgM	1.44	0.40–3.00

3. Discussion

IgG4-RD is diagnosed exclusively on histopathological analysis and the hallmarks of this disease are dense lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis [3]. IgG4-RD has only been recognised as a separate and collective entity in the last two decades in the medical literature [4]. Synchronous or metachronous manifestation of IgG4-RD can occur in single and/or multiple organs [5]. Graves' disease is not related to IgG4-RD even though certain thyroid disease such as Riedel's thyroiditis and Hashimoto's thyroiditis are considered a spectrum of IgG4-RD [6].

Serum IgG4 levels, tissue quantification of IgG4+ plasma cells or ratio of IgG4:IgG levels are only supportive of the diagnosis [7]. A serum IgG4 level greater than 135 mg/dL or a ratio of IgG4: IgG greater than 40% is not regarded as diagnostic for IgG4-RD [8]. Elevation of serum IgG4 level can be found in patients who had immunotherapy, atopic diseases or parasitic diseases [9].

Aetiology of the disease remains an enigma but an autoimmune process has been stipulated as a potential cause [10]. Immunoglobulins are glycoproteins produced by plasma B cells and plays a crucial role in immunity. Even though immunoglobulin G (IgG) is the most abundant isotype in blood (70–75%), IgG4 accounts for only 3–6% of total IgG [11].

To date, there is ten cases of IgG4-RM and this is shown in Table 2. The average age of affected patients is 57 years. There is no reported cases of IgG4-RM in men. Lesions are often palpable but painless. The lesions can appear as a single lesion or multiple lesions affecting one or both breasts. Four patients in this case series had concurrent IgG4-RD at other sites apart from breast and this is consistent with the reported literature [12,13]. IgG4-RM has excellent prognosis after limited excision or steroid therapy [14–17].

Imaging features of IgG4-RM are scarce. Such mammography appearance does not discriminate between benign nor malignant breast lesions and important differentials to consider should

Table 2
A summary of key clinical features, investigations and treatment outcomes for cases reported in the literature.

References	Case/Demographics	Symptoms	Lesion/Laterality	Serum levels	Tissue IgG4/IgG plasma HPF	Extra-manifestations	Treatment	Outcomes
[12]	F/48	Painless Palpable	Multiple Bilateral	IgG4 350 mg/dL (0–135)	272/421 (65%)	N/A	Excision	No recurrence at 1 year
[12]	F/51	Painless Palpable	Multiple Right	IgG 3900 mg/dL (2300–3600)	405/479 (85%)	Unilateral eyelid swelling (previous)	Excision	No recurrence at 3 years
[12]	F/37	Painless Palpable	Multiple Right	Rheumatoid factor 29 IU/L (0–20)	383/467 (82%)	Diffuse lymphadenopathy (cervical, axillary, inguinal) (present)	Observation	Resolution of breast lesion at 6 months
[12]	F/54	Painless Palpable	Single Right	N/A	495/1005 (49%)	N/A	Excision	No recurrence at 11 years
[13]	F/46	Induration	Single Right	IgG4 185 mg/dL	N/A	N/A	Excision	No recurrence at 1 year
[14]	F/58	N/A	N/A	IgG4 920 mg/dL	N/A	Mikulicz syndrome AIP (current)	Excision Prednisolone	No recurrence at 7 months
[15]	F/51	Painless Palpable	Single Right	IgG4 217 mg/dL	N/A	Bilateral eyelid swelling (current)	Prednisolone	No recurrence at 7 months
[16]	F/66	Painless Palpable	Single Left	N/A	179/280 (63.9%)	N/A	N/A	N/A
[16]	F/45	Painless Palpable	Single Right	N/A	308/483 (67.3%)	N/A	N/A	N/A
[17]	F/61	Painless Non-palpable	Single Left	Rheumatoid factor 122 IU/L (0–29)	IgG+ >70% IgG4- 50 per HPF	Chronic sialadenitis (past) Non-alcoholic pancreatitis (past) Cervical mass (present)	N/A	N/A

include lymphoma, sarcoidosis and granulomatous disease of the breast [17].

Treatment of IgG4-RM with steroid is predominantly anecdotal. Steroid-sparing agents such as azathioprine, cyclosporin and even B-cell depletion therapy has been reported in the literature but is experimental [18]. Radical surgery or interventional radiology are reserved for cases such as IgG4-aortitis causing aneurysms or hydronephrosis secondary to IgG4-retroperitoneal fibrosis [19].

4. Conclusion

IgG4-RM is rare and is diagnosed primarily through histopathological analysis. Limited surgical excision is useful as it is both diagnostic and therapeutic. Clinicians who are aware of this condition will make better treatment decisions for patients affected with IgG4-RM or IgG4-RD. Patients with clear symptoms of IgG4-RD should proceed to have further investigations. However, extensive imaging in an asymptomatic patient is not considered prudent.

Conflict of interest

There is no conflict of interest to declare.

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Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

ET drafted the manuscript and collected the relevant patient data.

BF, SL and JP contributed to further writing and editing of the manuscript.

Registration of research studies

Not applicable.

Guarantor

Dr. Ee S Tan.

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