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## CASE REPORT

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# Immunoglobulin G4-related Sclerosing Disease of the Breast and Skin in a Male Patient

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### ABSTRACT

*Immunoglobulin G4 (IgG4)-related disease affects multiple organs and is characterised by an increase in serum IgG4 concentration, IgG4-positive plasma cells, lymphocytic infiltration, inflammation, and fibrosis. Its aetiology remains unknown. We describe the first male patient with simultaneous involvement of the breast and skin. Mammography, ultrasonography, and magnetic resonance imaging revealed an index mass with multiple nodules in the left breast and skin nodules. Cancer was excluded radiologically, and image-guided biopsy of the breast and skin lesions showed many plasma cells within the lesions immunohistochemically positive for IgG4. The patient also had a raised serum IgG4 titre. The diagnosis of IgG4-related sclerosing disease was confirmed. We describe the imaging and pathological features of this entity in breast and skin. It should be considered a differential diagnosis of a breast lesion and can mimic malignancy. Biopsy for histological confirmation is advocated. It has good response to systemic steroid therapy, and unnecessary surgery can be avoided.*

*Key Words: Breast neoplasms; Immunoglobulin G; Mastitis*

## 中文摘要

### 一位男性患者乳房皮膚免疫球蛋白G4相關性硬化症疾病

譚家盈、陳慧儀、譚國輝、周慧璇、鄧佩儀

免疫球蛋白G4 (IgG4) 相關疾病能影響多個器官，其特徵是血清IgG4濃度增加、IgG4陽性漿細胞增加、淋巴細胞滲透、炎症和纖維化。其病原仍然未知。我們描述首例男性乳腺和皮膚的IgG4相關疾病。乳房X線照相、超聲檢查和磁共振成像顯示主瘤與多個結節在左乳房和皮膚。影像學檢查排除癌症，影像學引導乳房和皮膚組織活檢顯示病變內許多漿細胞免疫組織化學IgG4呈陽性，患者的血清IgG4滴度亦上升。我們描述此疾病的乳房和皮膚影像和病理特徵。它可表現類似惡性腫瘤，是乳腺病變的一個鑑別診斷。建議組織活檢檢查斷診。此病對類固醇治療有良好的反應，應避免不必要的手術。

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## INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease is a collection of disorders that share specific pathological, serological, and clinical features.<sup>1</sup> Its aetiology remains unknown. Six cases of IgG4-related sclerosing mastitis in female patients have been reported with a focus on the pathological aspect.<sup>2</sup> We report the first male patient with IgG4-related disease of the breast and skin and present comprehensive radiological and pathological findings. Patient consent to publication was obtained.

## CASE REPORT

In June 2013, a 53-year-old man presented with a 3-month history of a palpable lump in the left breast. He had a history of hypertension, diabetes, and carcinoma of the appendix (T4N1 disease), for which he underwent right hemicolectomy in 2000. The left breast lump was not painful, and there was no nipple discharge or skin ulceration. The patient had no previous major trauma, fever, family history of breast cancer, or use of hormones. On physical examination, the 4-cm hard mass was located at the 10 o'clock position 3 cm from the nipple of the left breast. Skin discolouration with rash and skin nodules were noted at the left chest wall (Figure 1). The right breast was unremarkable. No enlarged axillary lymphadenopathy was detected. Complete blood count, liver and renal function tests, and inflammatory markers were normal.

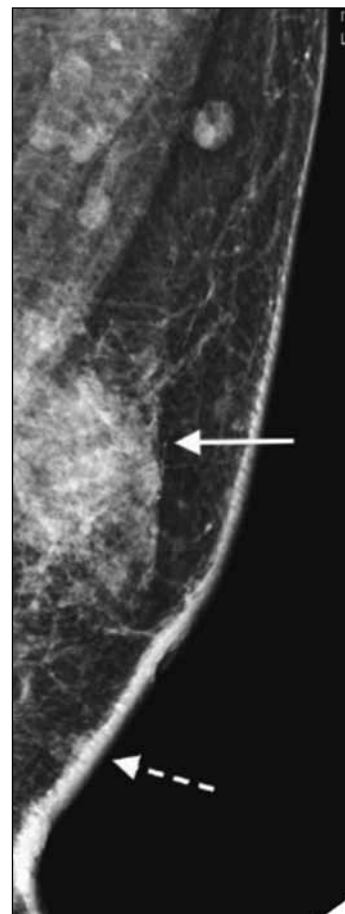
Mammography showed a 5-mm medium density area with ill-defined margin at the upper inner quadrant of the left breast, with multiple prominent lymph nodes at the



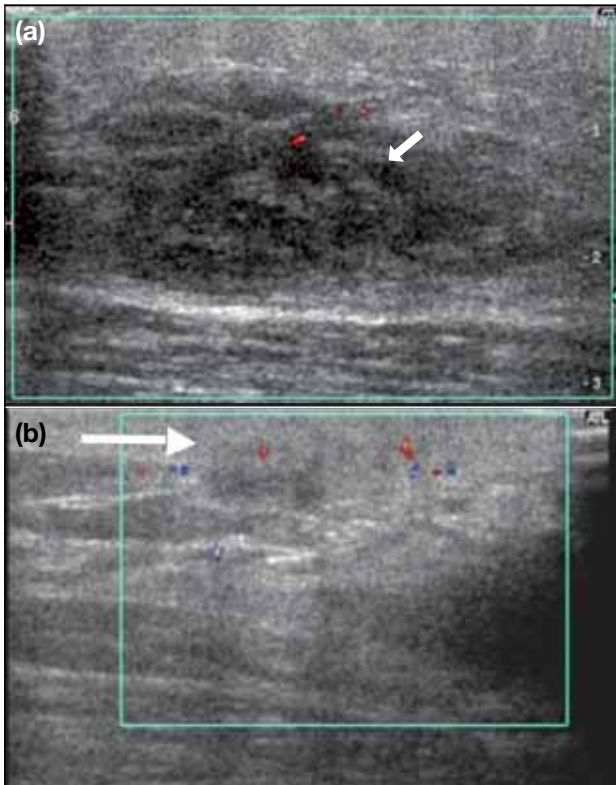
**Figure 1.** Skin discolouration with rash and skin nodules at the left chest wall.

left axilla (Figure 2). No clustered microcalcifications were detected. The skin and nipple-areolar complexes were unremarkable. No focal abnormality was detected on the contralateral side. Ultrasonography of the breasts showed a 3.5-cm hypoechoic mass with partially microlobulated and irregular margin but with no internal hypervascularity, as well as multiple small hypoechoic nodules adjacent. The overlying skin was thickened with multiple skin nodules of mild peripheral vascularity (Figure 3). Magnetic resonance imaging (MRI) showed the mass with T1-weighted hypointense and heterogeneous short-tau inversion recovery (STIR) signals with a hyperintense rim and hypointense centre, and a low apparent diffusion coefficient value at the centre, and multiple enhancing nodules infiltrating the subjacent skin (Figure 4). It showed heterogeneous enhancement and a type 2 kinetic curve. No focal abnormality was detected in the right breast.

Results of fine-needle aspiration of the index mass were inconclusive. Core biopsy was performed using

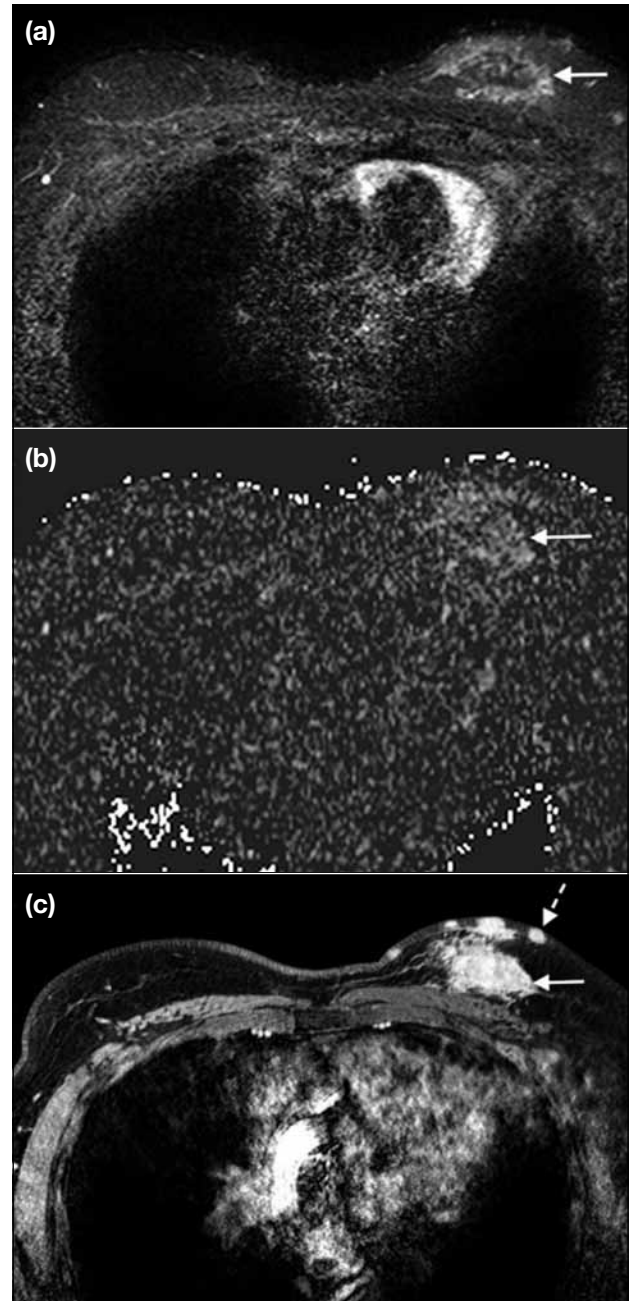


**Figure 2.** Mammography showing a medium density with ill-defined margin at the upper inner quadrant of left breast (arrow), subadjacent skin thickening suggestive of skin involvement (dash arrow), and multiple prominent roundish lymph nodes at the left axilla.



**Figure 3.** Ultrasonography showing (a) a hypoechoic mass (arrow) with partially lobulated and irregular border at the 10 o'clock position in the left breast, with no internal hypervascularity, and (b) skin thickening with hypoechoic nodules (arrow) at the dermo-subcutaneous junction with mild peripheral vascularity.

a 14-gauge Max-Core and Magnum biopsy needles for the mass and skin nodules, respectively. Fine-needle aspiration of the left axillary lymph nodes was also performed. Pathological examination of the index mass showed cores of fibroadipose tissue with dense lymphoplasmacytic infiltrate and some histiocytes, as well as sclerosis and reactive fibroblastic proliferation (Figure 5). The plasma cells were mostly of IgG subtype. The absolute number of IgG4+ cells increased to 80 per high-power field and IgG4+ / IgG+ plasma cells equalled 40%. There was no nuclear atypia or malignancy. The diagnosis of IgG4-related sclerosing disease of the left breast and skin was confirmed. Aspiration of the left axillary lymph node showed mixed lymphoid cells with predominant small lymphocytes. The serum IgG4 titre increased to 1830 (normal: 61-1214) mg/l. The C3 and C4 levels were normal. Contrast-enhanced computed tomography of the thorax, abdomen, and pelvis showed no other organ involvement. Thyroid ultrasonography was also unremarkable.



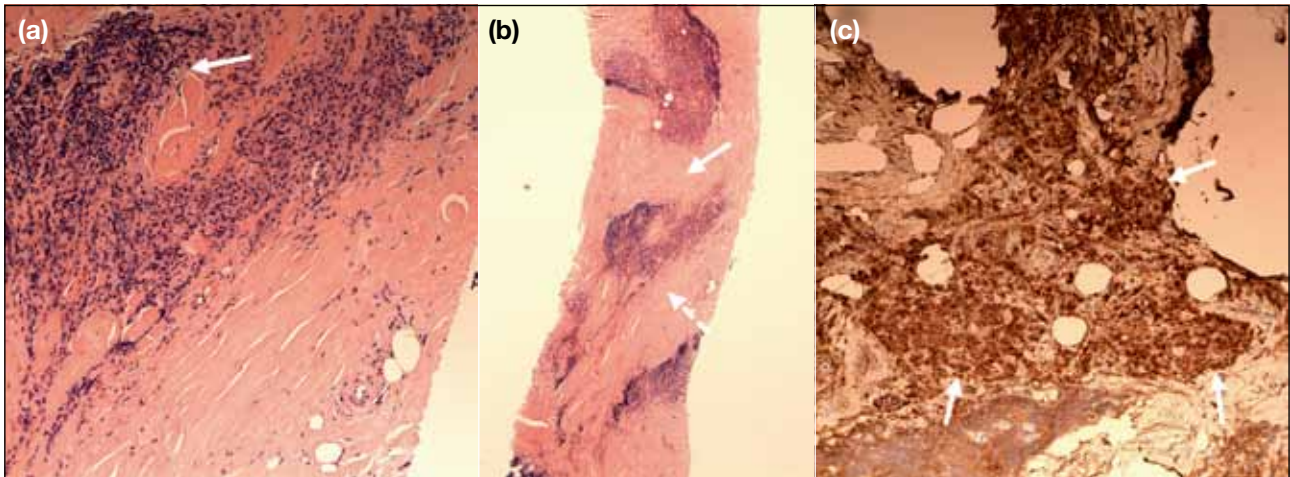
**Figure 4.** Magnetic resonance imaging showing the index irregular mass (arrows) in the left breast with (a) heterogeneous short-tau inversion recovery hyperintense signal, (b) low signal on an apparent diffusion coefficient map, and (c) significant enhancement and multiple enhancing nodules infiltrating the skin (dash arrow).

The patient refused surgical excision and steroid therapy, and is currently on conservative treatment.

## DISCUSSION

### Epidemiology

There have been six case reports of IgG4-related



**Figure 5.** (a) Dense lymphoplasmacytic infiltrates (arrow) within the sclerotic stroma (H&E, x400), (b) marked fibrosis (arrow) and patchy lymphoplasmacytic infiltrates (dash arrow) in the breast tissue (H&E, x100), and (c) plasma cells positive for immunoglobulin G4 immunostaining (arrows) [H&E, x400].

sclerosing disease of the breast in female patients aged 37 to 54 years. All presented with single or multiple painless palpable masses in the breast for a few months, with or without evidence of systemic IgG4-related disease. We report the first such case in a male patient and describe it as ‘inflammatory pseudotumour’ or ‘sclerosing mastitis’. IgG4-related disease usually occurs in middle-aged and older men, but the sex distribution depends on the index manifestation. For example, IgG4-related pancreatitis occurs more often in older men, whereas IgG4-related sialadenitis shows more equal sex distribution.<sup>3-5</sup>

Skin involvement can be a part of systemic involvement or an isolated lesion. The lesions commonly present as ill-defined erythematous patches, or solitary or grouped erythematous papules or nodules, sometimes subcutaneous. These are mostly seen in the head and neck region, followed by the trunk and limbs. Cutaneous lesions mostly occur in men and in Asian ethnicity,<sup>6</sup> consistent with our patient. Histologically, it is characterised by dermal or subcutaneous nodular lymphoid infiltration with follicle formation and stromal fibrosis. The infiltrate is rich in IgG4 plasma cells, small lymphocytes, and sometimes plasmablasts and eosinophils.<sup>7</sup> The differential diagnoses include other lymphoproliferative conditions (e.g. pseudolymphoma cutis, B cell lymphoma, Wegener granulomatosis, and sarcoidosis), skin metastasis, primary skin malignancy (e.g. basal cell carcinoma or amelanotic melanoma),

lupus rash, and infection (e.g. syphilis). Therapeutic options include immunosuppressive agents such as corticosteroid, azathioprine, rituximab, and infliximab. Surgery can be considered in refractory cases.<sup>6</sup>

### Pathology

IgG4-related sclerosing disease is an idiopathic chronic inflammatory disease. The disease can involve systemic and different organs including the breast.<sup>8</sup> The IgG4+ plasma cell count is an important histopathological feature. Its key morphological features are (1) lymphoplasmacytic inflammation, (2) fibrosis that is at least focally storiform, and (3) obliterative phlebitis. Eosinophils may also be prominent although this is variable. The diagnosis can be confirmed on immunohistochemistry by prominent IgG4+ plasma cells within the inflammatory cell infiltrate, and the ratio of IgG4+ plasma cells to the total number of IgG+ plasma cells of  $\geq 40\%$ . The pathological findings are elevated serum levels of IgG4,<sup>9</sup> although  $<40\%$  of patients have normal serum IgG4 concentrations despite the presence of the classic histopathological changes in tissue.<sup>10</sup> With histiocytic infiltration, differential diagnoses include Langerhans cell histiocytosis, granulomatous lobular mastitis, Erdheim-Chester disease, and IgG4-related sclerosing disease.<sup>8</sup> Compared with lymphocytic mastitis and granulomatous mastitis, IgG4-related mastitis shows denser IgG4+ plasmacytic infiltration with higher IgG4/IgG ratio,<sup>2,9,11</sup> as seen in our patient. It responds well to steroid therapy, especially in patients with limited fibrosis.<sup>2,12</sup>

## Imaging Features

IgG4-related disease can simulate breast malignancy, as in our patient with a medium density mass with irregular margin. Associated skin infiltration simulated skin thickening in lymphoedema, and ultrasonography revealed an irregular hypoechoic mass. Yet, there was no hypervascularity in the lesion contrary to that seen with high-grade breast cancer, as this disease does not involve neovascularisation or angiogenesis. Instead, it involves considerable extent of obliterative phlebitis. In our patient, MRI revealed heterogeneous high STIR signal and low signal in the apparent diffusion coefficient map. The lesion showed significant contrast enhancement and a non-specific kinetic curve. There is usually concurrent nodal involvement. It can mimic breast malignancy clinically and radiologically. Hence, excision or core needle biopsy should be performed for diagnostic treatment.<sup>13</sup>

According to the American College of Radiology, the main indications for use of contrast-enhanced MRI of breasts are (1) high-risk patients with >20% lifetime risk of breast cancer such as those with a genetic predisposition to breast cancer by gene testing or family pedigree, or those with a history of mantle radiation for Hodgkin's disease, (2) occult new malignancy in the contralateral breast of newly diagnosed breast cancer patients, (3) patients with breast augmentation, and (4) assessment of extent of disease before and after treatment including lumpectomy or neoadjuvant chemotherapy. In our patient, the indication was for lesion characterisation. Breast MRI may be indicated when other imaging modalities and physical examination are inconclusive, and biopsy cannot be performed.<sup>14</sup> In our patient, the lesion appeared atypical for male breast cancer and fine-needle aspiration was initially inconclusive. Excision biopsy for the lesion was recommended. MRI was then arranged for lesion characterisation and screening for any potential lesion in the contralateral breast. Biopsy was performed after MRI confirming the diagnosis of IgG4-related sclerosing disease.

## Management

Diagnostic criteria for IgG4-related disease are (1) raised serum concentration of IgG4 (cut-off at 135 mg/dl) and (2) histopathological findings of marked IgG4-positive cell infiltration (>10 cells per high-power field and IgG4+/IgG+ cell ratio >40%). Although some patients with solitary organ involvement may have normal serum IgG4, elevated serum IgG4 titre seems to

be a marker for systemic involvement.<sup>15-17</sup>

The broad spectrum of IgG4-related sclerosing disease should prompt a search for systemic manifestations to avoid misdiagnosis and unnecessary surgery.<sup>18</sup> In our patient, contrast-enhanced computed tomography of the thorax, abdomen, and pelvis, together with ultrasonography of the neck were performed to investigate other organ involvement. The incidence of malignancy in IgG4-related disease is similar to that in the general population.<sup>19</sup> Nonetheless, three cases of localised lymphoma arising from IgG4-related chronic sclerosing dacryoadenitis have been reported,<sup>7</sup> as have three cases of lymphoma in 111 patients with IgG4-related disease. Several cases of ductal pancreatic adenocarcinoma have also been described in association with IgG4-related sclerosing pancreatitis. Further work is required to ascertain whether there is a causal relationship or risk in developing malignancy in IgG4-related disease.<sup>7</sup>

<sup>18</sup>F-fluorodeoxyglucose positron emission tomography-computed tomography enables whole-body image acquisition and assessment of disease activity. It has not been well established for assessment of IgG4-related disease, but may have a role in staging disease, guiding biopsy, and monitoring response to treatment. Clinical, laboratory, imaging, and histological findings should also be taken into account for diagnosis. More studies are required to determine its cost-effectiveness and clinical impact in this disease.<sup>20</sup>

## CONCLUSIONS

IgG4-related mastitis can mimic breast malignancy. Core biopsy or surgical excision for histological confirmation is advocated, as is correlation with serology. Positron emission tomography-computed tomography may play a role in investigating organ involvement and disease staging and management.

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