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A RARE CASE OF IGG4-RELATED DISEASE CAUSING INFLAMMATORY BREAST MASS SUCCESSFULLY TREATED WITH ANTI-CD20 BIOLOGICAL THERAPY: A DISCUSSION OF CLINICAL CASE WITH LITERATURE REVIEW

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ABSTRACT

We report a rare yet successful utilisation of anti-CD20 therapy using rituximab for treatment of a case of IgG4-related mastitis proven by clinical, serological, and histopathological evidence. This was affecting a mid-aged female who was referred to the rheumatology clinic by the breast surgeons to help assessing for the possibility of an underlying inflammatory process involving the breast tissue unilaterally.

The clinical course was apparently complex with an onset of an induration in the right lateral superior quadrant of the breast with mild discomfort and heaviness sensation. This increased over a course of 2 weeks before presentation to the general surgery clinic.

Subsequent investigations confirmed that the case was IgG4-related mastitis and a trial of steroids and disease modifying anti-rheumatic drugs (DMARDs) was partially helpful, but not to a full degree, mandating the utilisation of a more advanced mode of therapy, so rituximab was selected.

KEYWORDS

IgG4-related disease, inflammatory lump, biological therapy, rituximab, anti-CD20 therapy

LEARNING POINTS

- Consider inflammatory conditions including IgG4-related disease in the differential diagnosis of lumps including breast masses.
- IgG4 disease is a rare condition but can have complex clinical course and significant complications that need a low threshold of suspicion in terms of diagnosis.
- Occasionally, a repeat study and re-reading of histopathological specimen with appropriate immunostaining can open the way for accurate diagnosis in challenging cases with an unreached diagnosis.

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INTRODUCTION

IgG4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory disorder characterised by dense lymphoplasmacytic infiltrates with a high percentage of IgG4-bearing plasma cells, abundant storiform fibrosis, obliterative phlebitis and frequent tissue eosinophilia[1].

Greater awareness of this disease is needed to ensure earlier diagnosis, which can prevent severe organ damage, disabling tissue fibrosis and even death[2].

Clinical presentation varies widely and depends on the organs involved (e.g. pancreas, salivary and lacrimal glands, retroperitoneum, lymph nodes, lungs, kidneys and aorta)[3].

IgG4-related mastitis is a rare presentation of this condition. The few case reports highlighting this presentation usually mention malignancy as one major differential diagnosis[4].

CASE DESCRIPTION

A 30-year-old female was referred to the rheumatology clinic by the breast surgeons to help assessing for the possibility of an underlying inflammatory process in the case of the subject with symptoms related to the breast tissues. The clinical course was complex with an onset of an erythematous induration in the lateral area of the breast adjacent to the areolar region, associated with mild discomfort sensation. It increased over a course of a week before presentation to the general surgery clinic. On initial physical examination by the surgeons, she was found to have erythematous induration at the 9 o'clock location for which she initially underwent an in-clinic ultrasound scan suggestive of possible collection *(Fig. 1)*. This was acted on by performing incisional drainage and submitting the samples for fine-needle aspiration and microbiological cultures, but 10 days later she developed a recurrence of the induration with some minimal swelling. The patient initially received 10 days empirical course of ampicillin-based oral antibiotic. The results of all cultures were unremarkable. The patient subsequently underwent incisional biopsy including the affected area only. This was again complicated with further recurrence. The surgical team accordingly arranged a repeat breast ultrasound scan which showed a 2.5 × 2.6 cm superficial anechoic fluid collection within the retro-areolar area. Marks for the previous surgical intervention were surrounded by scattered free fluid and minimal changes of ductal ectasia and multiple subcentimetric left axillary lymph nodes, but with preserved fatty hilum. The patient noticed poor healing of the scars and she was re-assessed by the surgeons, who decided to refer her to the rheumatology service. On clinical assessment in rheumatology outpatients, we reviewed the case history. A systemic inquiry was conducted to screen for presence of any of the symptoms that may exist in auto-immune inflammatory condition, but this was on the whole unremarkable. There was an absence of any constitutional symptoms and no presence of any rashes, fever, lymphadenopathies, hepatosplenomegaly, synovitis, or vasomotor findings. Further investigations were arranged including updated figures for the acute phase reactants

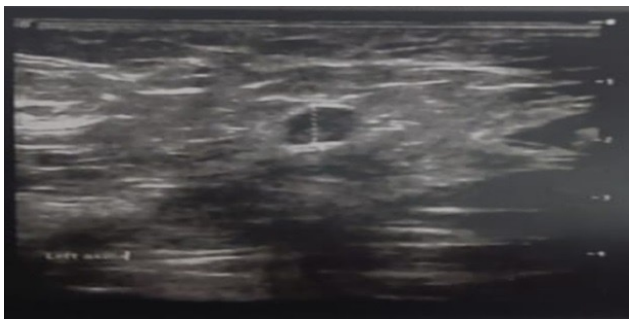

Figure 1. Ultrasound scan showing the described fluid collection within the left retro-areolar area of the left breast.

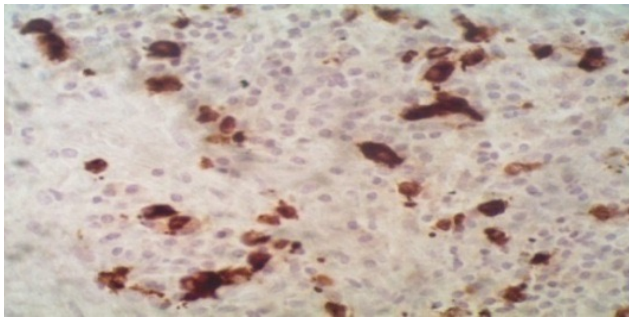

Figure 2. Histopathology analysis showing proliferation of lymphoid tissue, with increased plasma cells with fibrosis. Obliterative arteriolopathy was also present. The increase of plasma cells was IgG type.

(C-reactive protein - CRP, erythrocyte sedimentation rate - ESR) in addition to antinuclear antibody (ANA), serum calcium, TB screen by quantiFERON - TB Gold assay as well as IgG subclasses. It was also agreed to re-examine the histopathological specimens with a focus on obtaining appropriate immunostaining. The results of the arranged blood tests showed unremarkable blood counts but raised inflammatory markers ESR 48 and CRP 31.4 (normal <5). The quantiFERON - TB Gold blood test was unremarkable. ANA 1:160 speckled pattern with negative extractable nuclear antigen panel components and C3/C4 components were unremarkable. The serum IgG4 level was however raised at 19.97 (normal range 7-16); the IgG4 subclass was raised at 2.1 g/l. A urine sample was screened for proteinuria, but the result was within normal range. A chest X-ray and abdominal ultrasound scan were unremarkable. These were followed up by a completed neck, chest, abdomen, and pelvis CT scan, which were all unremarkable. The histopathology result came back showing that there was no evidence for malignant tissues but presence of dense breast tissue *(Fig. 2)*. The retro nipple area showed proliferation of lymphoid tissue, with increased plasma cells with fibrosis. Obliterative arteriolopathy was also seen. The increase of plasma cells was IgG type. It was found that 22% of IgG-positive cells were of IgG4 type, consistent with IgG4 disease process.

On having the diagnosis of IgG4-related mastitis confirmed *(Table 1)*, a consensus of a treatment plan was established. It was agreed to start with a course of steroids encompassing prednisolone, starting at a daily 40 mg dose by mouth tapered down over a course of 6 weeks. During this period,

Type	Criteria details
Clinical criteria	Diffuse/localized, masses/nodules in sin-gle/multiple organs characteristic of IgG4-RD
Hematologic criteria	Elevated IgG4 concentration (>135 mg/dl)
Histopathologic criteria	1. Lymphocyte and plasma cell infiltration and fibrosis 2. Ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasmacella/Hpf 3. Typical tissue storiform fibrosis or oblitera-tive phelbitis

Note: This is a. combination of organ-specific diagnostic criteria. Patients with a possible or probable diagnosis by comprehensive diagnostic criteria who fulfil the organ-specific criteria for IgG4-RD are regarded as being definite for IgG4-RD[5].

Table 1. The 2020 revised comprehensive diagnostic criteria for IgG4-RD.

towards the fourth month, the patient started to feel that the induration, ache, and erythema were starting to improve. However, there was no full resolution. The course of steroids was adjusted by reverting to the baseline dose and re-tapering down to maintain the favourable result, which was achieved, but again with no full resolution. It was agreed to start adding on a disease modifying anti-rheumatic drug (DMARD) and the selection was in favour of azathioprine, considering multiple factors among which were plans for conception once the pathological process was eliminated. Once monthly reviews were obtained and towards the fourth month of treatment there was still considerable improvement, but with residual fluid collection and induration. We discussed the possibility of utilising rituximab, which was subsequently administered in one-gram fortnightly doses, copying the rheumatoid arthritis protocol after appropriate screening and preparations. The rest of the DMARD plan was continued normally. On reviewing the result at 6 weeks there was further but significant improvement; by the tenth week, all symptoms resolved, and the breast tissue went back to normal without any recurrences, to the extreme satisfaction of the patient. The inflammatory markers were repeated, and CRP remained normal on repeated monthly samples, signalling excellent response to the anti-CD20 modality of treatment in this refractory case.

DISCUSSION

It was noticed from the clinical details of this case that the suspicion of an underlying inflammatory process involving the breast tissue was valid. There was a lack of evidence for malignancy and a poor response to treatment, with no convincing alternative diagnosis. The clinical course was complex, and the degree of emotional and depressive effects of such a problem in a young female who was in the process of starting a family could be expected. It is important in such cases to keep a low index of suspicion and to work on applying thorough and expert histopathological studies. It is also important to keep in mind that the diagnosis of IgG4-RD should be approached with the diagnostic criteria in mind, and that minimal elevation in IgG4 subclass is not enough to establish a diagnosis by itself. In terms of treatments, it is noticed that this varies according to the clinical presentation and the preferences of the treating physicians. We should bear in mind that there are different presentations of this rare condition. Systemic glucocorticoids are currently the first-line approach for IgG4-RD, and the indications are symptoms. The initial recommended dose of oral prednisolone for induction of remission is 0.6 mg/kg/day, administered for 2–4 weeks. This dose is gradually tapered to a maintenance dose of 2.5–5 mg/day over a period of 2–3 months[6]. IgG4-RD is prone to recurrence, and the risk of recurrent disease increases with the number of organs affected at baseline, and the baseline serum IgG4 concentration. Azathioprine, mycophenolate mofetil, methotrexate, leflunomide and cyclophosphamide are commonly used worldwide in combination with glucocorticoids in patients with IgG4-RD[7]. Case series suggest that B-cell depletion therapy is an effective treatment in many of the patients with IgG4-RD that is refractory to glucocorticoids and other medications. A retrospective nationwide study in France showed that rituximab was effective as both induction and maintenance treatment. Relapses occurred when rituximab was discontinued[8]. In our case, we used a step-up approach starting from a couple of courses of oral steroids, followed by DMARD add-on therapy that was followed by rituximab, which helped securing sustainable remission as described above.

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