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IgG4-Related Disease, a Systemic or Local Disease: This is the Problem

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ABSTRACT

Background: Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory condition that forms tumefactive lesions in various organs, presenting with diverse clinical manifestations. Diagnosis of IgG4-RD could be challenging and relies on characteristic histopathological findings and elevated IgG4+ plasma cell counts.

Case Presentation: The patient was a 48-year-old woman with diabetes mellitus initially presented with a painless breast mass. Imaging indicated irregular opacities and lymph nodes in the breast. Biopsy results revealed lymphoplasmacytic infiltration with IgG and IgG4 positivity, overall compatible with IG4-related disease. A mass resection was performed, and intraoperative assessment ruled out malignancy. Then, with a 5-month interval of no symptoms, the patient developed a cheek mass, initially misdiagnosed as low-grade spindle cell sarcoma. Subsequently, she underwent partial maxillectomy, further examination, and histology confirmed IgG4-RD, meeting all diagnostic criteria.

Conclusion: This case underscores the diagnostic challenges posed by IgG4-RD, often mistaken for malignancies due to its invasive behavior and emphasizes the importance of considering IgG4-RD in differential diagnoses for tumor-like lesions, particularly when affecting multiple organs, to enable timely treatment decisions and prevent unnecessary interventions.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a newly described fibroinflammatory condition with a tendency to form mass lesions at multiple sites.[1] IgG4-RD was first recognized after a connection between elevated serum IgG4 levels and inflammatory mass lesions in the pancreas leading to autoimmune pancreatitis,[2] but it has been described as a disease with the ability to involve every organ system, including the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, aorta, breast, prostate, thyroid and skin.[1]

IgG4-RD is a rare, systemic fibroinflammatory condition with potential to mimic neoplastic processes. While IgG4 serum levels can be elevated, they are not a reliable diagnostic criterion. The two main features of IgG-related disease are an elevated number of IgG4-positive plasma cells within the tissue and a characteristic histopathological appearance including a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. Diagnosis is based on the balance of clinical features, histopathology, and serum markers.

IgG4-RD usually affects individuals of middle to upper age, with an onset at 50–70 years and is more

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common in males, especially for IgG4-related pancreatitis; however, IgG4-related sialadenitis and dacryoadenitis may occur more frequently among females.[3,4] It is a complex disease with highly variable clinical manifestations, that can mimic other inflammatory and neoplastic conditions. The diagnosis of IgG4-related disease rests on the combined presence of the characteristic histopathological appearance and increased numbers of IgG4+ plasma cells. These histopathologic features include a dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis.[1]

Although the most frequent localizations of IgG4-RD following the pancreas are head and neck region[3] with the most common subsites including the orbit, salivary gland and lacrimal gland[5], maxillofacial involvement and soft-tissue lesions of head and neck region have not been commonly reported. Here we report a challenging case of IgG4-RD with two relatively rare and metachronous manifestations of the disease, breast and head and neck involvement which mimicked malignancy.

CASE PRESENTATION

A 48-years-old woman, a case of diabetes mellitus, presented with one-month history of palpable painless mass of right breast without significant overlying skin changes. Mammography revealed an irregular focal opacity in UOQ of the right breast with multiple lymph nodes in both axilla. The following ultrasound showed multiple ill-defined solid hypoechoic masses with irregular border measuring 19x17mm at the tail of the right breast (BIRADS 5) with reactive lymph nodes being the largest measuring 15x7mm at right axilla.

Subsequently, an ultrasound-guided core needle biopsy was done in another center and reported as breast tissue with marked infiltration of mixed inflammatory cells including PMNs, histiocytes and lymphocytes, some of which showed positive immunoreaction for CD3 and CD20 (acute inflammatory process). Then, she was referred to our center and underwent a mass resection. Due to the suspicion of a malignant mass by the surgeon during surgery, axillary sentinel lymph nodes biopsy was done and intraoperative pathologic consultation was requested for the nature of the mass which was not malignant in frozen section studies and reported as an inflammatory process. On gross examination, the specimen measured 14x13x6cm with overlying skin measuring 12x5cm. On cutting, a unifocal tan-brownish firm mass measuring 3.5x3x3cm with irregular borders was noted. Microscopic examination showed numerous inflammatory cell infiltrations with round and variable-sized nodular gross patterns, containing interlacing bundles of myofibroblasts in close contact with many inflammatory cells predominantly composed of lymphoplasmacytic cells admixed with few neutrophils and histiocytes. Also, phlebitis obliterans and fat necrosis infiltrated by foamy macrophages and other inflammatory cells were noted (Figure 1). No margin involvement was identified.

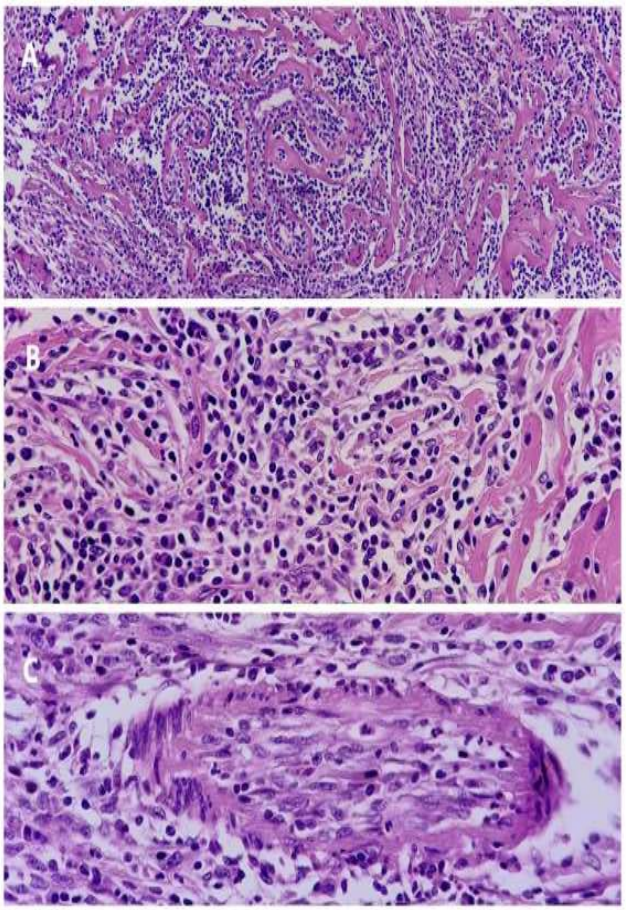

Figure 1. H&E staining showing (A & B) (10x & 40x) nodular heavy aggregates of inflammatory cells mostly lymphoplasma cells within breast tissue with collagenized stroma and (C) (40x) phlebitis obliterans

Immunohistochemistry studies showed CKAE1/AE3, ALK and P63 negative staining and many plasma cells with positive IgG and IgG4 (Figure 2). Overall findings were compatible with IgG4-related disease. Five-month follow-up showed no evidence of recurrence.

Five months later, she presented with left 78 cheek and suborbital swelling and pain accompanied by skin erythema. Head and neck examination demonstrated left suborbital mass with tenderness. General examination was unremarkable. A computed tomography study showed a soft tissue mass extending from the lateral wall of the nasal cavity to the left maxillary bone and infraorbital region, measuring 30x18x15mm with an ill-defined periphery and increased density of subcutaneous fat.

Also, increased mucosal thickness and erosion of the anterior wall of the left maxillary sinus were seen.

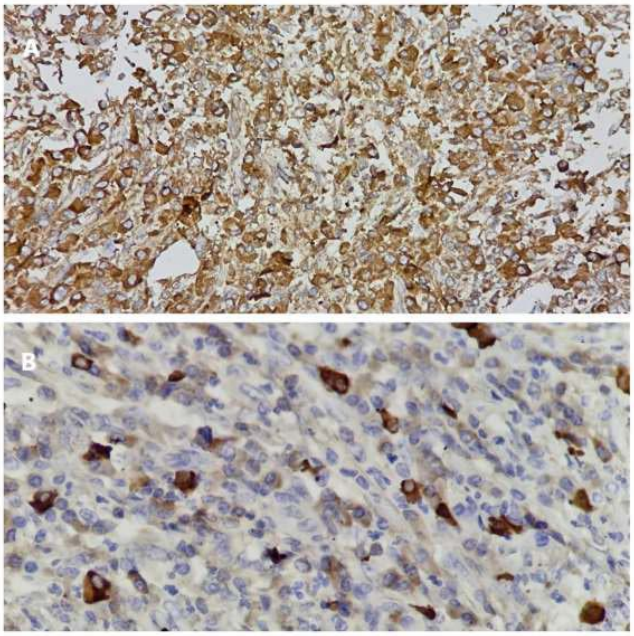

Figure 2. (A) (40X) Many plasma cells with positive fine granules of immunoglobulin (IgG) (B) (40x) about 50% of them were stained with IgG4 in the IHC study

The incisional biopsy of the maxillary lesion was reported as "low-grade spindle cell sarcoma, consistent with low-grade myofibroblastic sarcoma" in another center. Therefore, she was referred to our center and underwent a partial maxillectomy. Gross examination showed an ovoid piece of tissue measuring 6x4x2cm partially covered with skin, with an infiltrative tan mass measuring 4x2.5x2cm in cut sections. Microscopic examination revealed an inflammatory process composed of a storiform growth pattern of fibroblasts and many inflammatory cells specially lymphoplasmacytic cells surrounding some nerve bundles as well as foci of fat necrosis. Also, mild irregular lymphoid aggregates containing prominent large germinal active centers were observed (Figure 3). Furthermore, an immunohistochemical study was performed which showed negative staining for SMA, CKAE1/AE3, B-catenin, ALK and S100. Ki67 decorated background lymphoid cells. Also, many plasma cells were IgG positive, of which more than 40% were IgG4 positive (Figure 4), suggesting IgG4-related disease.

Serum IgG4 was not ordered preoperatively; however, the serum IgG and IgG4 levels postoperatively were 1244mg/dl and 73mg/dl, respectively, which were within normal ranges. She is now in follow-up by a rheumatologist and there has been no indication to initiate any form of immunosuppressive therapy for the management of her IgG4-RD given that she has had no other disease-related changes so far.

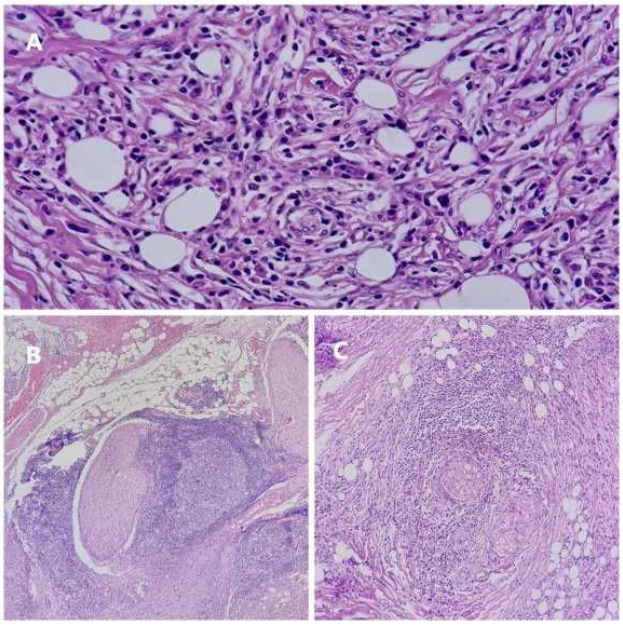

Figure 3. H&E staining showing (A) (40x) lymphoplasma cell dominant inflammatory process with the storiform pattern of fibrosis, (B) (4x) mild irregular lymphoid aggregate with visible germinal center, and (C) (10x) lymphoplasma cells surrounding nerve bundle.

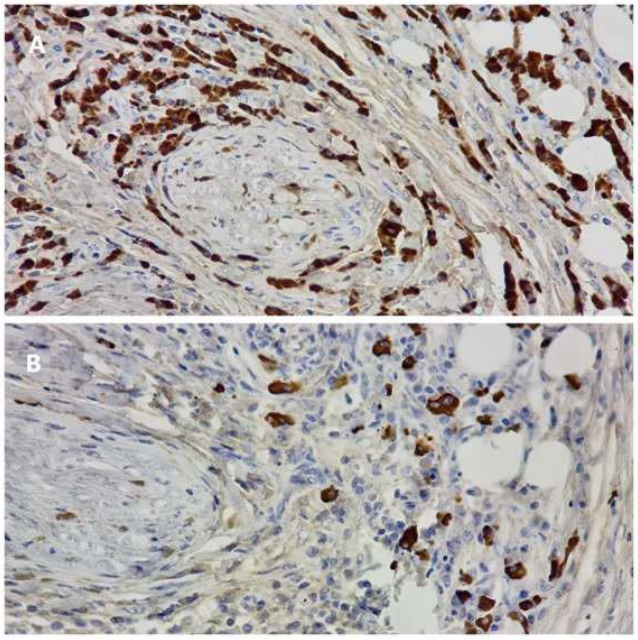

Figure 4. Immunostain for IgG and IgG4 shows (A) (40x) many IgG4-positive plasma cells with (b) (40x) more than 40% positive for IgG4

DISCUSSION

IgG4-related disease is a rare systemic fibro-inflammatory disease, abile to form inflammatory masses and mimic neoplastic processes. The pathophysiology of this condition is still not understood and no known role of the IgG4 molecule

itself has been identified. It is assumed that the inflammatory and fibrotic processes that drive IgG4-RD are propagated by a combination of Th2 cells and regulatory T cells.[5]

Based on a cohort of 235 Japanese patients with IgG4-RD, pancreatitis was the most frequent manifestation followed by sialadenitis, tubulointerstitial nephritis, dacryoadenitis and periaortitis.[3] The most common sites of presentation of IgG4-RD in the head and neck region are the salivary glands, lacrimal glands and periocular tissues, but soft-tissue involvement of the head and neck has not been commonly reported.[5]

According to an international consensus statement on the pathology of IgG4-RD, the two main features of IgG-related disease are a characteristic histopathological appearance and an elevated number of IgG4 positive plasma cells within tissue. The three major histopathological features of IgG4-RD include a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. Two other histopathological features associated with IgG4-related are phlebitis without obliteration and increased numbers of eosinophils. With the presence of two of the three major histological features, a confident pathological diagnosis can be stablished.[1] Our case meets all three major histopathological features.

In general, the IgG4 serum level is considered an unreliable diagnostic criterion. This is due to the fact that almost 40% of patients with a histologically confirmed IgG4-RD serum level of IgG4 fall within the normal range.[1] However, we should consider in this case that serum IgG and IgG4 level were evaluated almost a month after the mass was surgically removed and the patient had no active symptom of the disease. IgG4+/IgG+ plasma cell ratios in tissue >40% with 94.4% sensitivity, 85.7% specificity and >10 IgG4+ cells per HPF have been used for the diagnosis of IgG4-RD. Considering the decreasing trend of IgG4+ plasma cell concentrations in fibrotic tissue areas, it has been suggested that IgG4+/IgG+ plasma cell ratio is a better histopathologic cut off value than IgG4+ plasma cell number.[6]

Overall, a diagnosis of IgG4-RD should be based on the balance of clinical features, such as disease distribution throughout the body, clinical course, serum concentrations and histopathology.[6] IgG4-RD diagnosis can be challenging due to low prevalence and mimicking other diseases and it lies on the differential diagnosis of spindle cell tumors, lymphoproliferative disorders, pseudotumors, and infections from a histopathologic point of view. Although IgG4-RD is a benign process, it has a tendency toward invasive behavior, including bony destruction, perineural infiltration, and bone marrow infiltration, which often lead clinicians to suspect malignancy.[7] In this specific case, clinical manifestation, suspicious radiologic features (such as bony destruction in maxillary sinus) and gross appearance (infiltrative masses) tissue biopsy histopathologic evaluation led to the treatment of the patient as a malignant case.

As IgG4-related disease is a systemic disease that should be treated and followed by a specialist (preferably a rheumatologist). There is a possibility of recurrence and the patient needs long term immunosuppression. Now it is known that glucocorticoids are the first-line agent for remission induction in all patients with active, untreated IgG4-RD unless contraindications to such treatment are present[8] and they have largely been successful in attaining disease remission.

CONCLUSION

In conclusion, IgG4-related disease is a rare but increasingly recognized disease. Its diagnosis is challenging because of various clinical presentations and tendency to mimic malignancy. Therefore, this report is intended to add knowledge about this disease and emphasize that in patients with tumor-like lesions specially when occurring in multiple organs, IgG4-RD should be considered as a differential diagnosis while ruling out malignancies, because early diagnosis of this condition will help to have better treatment decisions, avoid organ damage and unnecessary interventions.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL CONSIDERATIONS

The patient singed an informed consent to present the detail of her pathology and medical findings in this medical journal.

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