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Case study

Salivary duct carcinoma arising in IgG4-related autoimmune disease of the parotid gland

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Summary Hyper IgG4 disease or IgG4-related sclerosing/autoimmune disease is a multisystem condition characterized histologically by fibrosis, lymphoplasmacytic infiltration, and abundant IgG4 plasma cells associated with raised serum IgG4 levels. We present a case of salivary duct carcinoma of the parotid gland in a background of chronic sclerosing sialadenitis that also involved the submandibular gland with associated regional lymphadenopathy. The serology showed raised total IgG levels of 16.3 g/L (reference range, 6.0-15.0) and raised IgG4 levels of 3.41 g/L (reference range, 0.07-1.70). The salivary duct carcinoma contained areas of dense fibrosis and abundant IgG4-positive plasma cells (>100 per high-power field [hpf]). The adjacent noncarcinomatous areas, submandibular gland, and regional lymph nodes also contained plasma cells immunoreactive to IgG4 with densities higher than 100/hpf. To the best of our knowledge, this case is the first documentation of malignancy occurring in a background of IgG4-related autoimmune disease of the salivary gland.

1. Introduction

The term *hyperIgG4 disease* or IgG4-related sclerosing/autoimmune disease [1,2] is a well-recognized condition with tumorlike enlargement of one or more exocrine glands or extranodal tissues. The common manifestations include autoimmune pancreatitis [3-7], chronic sclerosing sialadenitis (CSS) [8], idiopathic retroperitoneal fibrosis [9,10], and lymphadenopathy [11]. This disease was first recognized when raised serum IgG4 was documented [3] in autoimmune pancreatitis. The features of this disease include fibrosis, lymphoplasmacytic infiltration, and abundant IgG4-positive plasma cells and clinical improvement with steroid therapy. In the English literature, the occurrence of malignancy with hyperIgG4 disease has been described with cases of pancreatic carcinoma [12-14] and ocular adnexal lymphoma [15]. To the best of our knowledge, no malignancy has been described with IgG4-related CSS.

Herein, we report a case of salivary duct carcinoma arising in a background of IgG4-related CSS of the right parotid gland.

2. Case report

A 75-year-old Chinese man presented with a 1-year history of a slow-growing right-sided preauricular lump

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with more recently a progressive seventh nerve weakness. His background included a 10-year history of bilateral fluctuating submandibular swelling and 2-year history of right lacrimal gland swelling that appeared to improve. There was no reported, skin lesions, or prior steroid therapy. The serology demonstrated elevated IgG4 levels of 3.41 g/dL (reference range, 0.07-1.70) and raised total IgG levels of 16.3 g/L (reference range, 6.0-15.0). The magnetic resonance imaging scan revealed an ill-defined tumor in the superficial lobe of the right parotid gland with possible lymph node metastasis and bilateral submandibular and bilateral lacrimal gland enlargement. Fine-needle aspiration cytology of the parotid lesion was of poorly differentiated carcinoma and the submandibular lesion was of lymphoid hyperplasia. To determine whether the disease process would be amenable to primary radiotherapy, the patient underwent an initial open biopsy of the parotid mass, excision of the ipsilateral submandibular gland and adjacent nodes, and biopsy of the nasopharynx. Histologic examination of the parotid lesion showed poorly differentiated carcinoma. Light microscopy of the submandibular mass showed CSS. The right nasopharynx biopsy showed reactive lymphoid hyperplasia, confirmed on flow cytometry by a polyclonal proliferation of B cells. The patient was treated with a radical right parotidectomy with facial nerve sacrifice, partial temporal bone resection, and upper neck dissection and postoperative radiotherapy. Postoperative computer tomographic scan showed several small mediastinal nodes (<1 cm), which are considered benign but will be monitored.

3. Pathologic examination

The resected specimen consisted of a parotid gland measuring 60 × 55 × 25 mm with overlying preauricular skin ellipse of 18 × 45 × 17 mm. There was a well-circumscribed light brown tumor beneath the preauricular skin on the superior aspect of the parotid gland measuring 35 × 30 × 17 mm. There were multiple enlarged lymph nodes identified. The histologic sections of parotid gland (Fig. 2A-D) showed infiltrative tumor composed of cribriform structures with central necrosis. There were also strands of tumor cells surrounded by dense fibrosis and abundant plasma cells. The tumor was composed of malignant epithelial cells with abundant cytoplasm and pleomorphic nuclei. The histologic features seen were in keeping with salivary duct carcinoma. There was lymphovascular space invasion and nerve involvement with no evidence of pleomorphic adenoma. The adjacent salivary gland showed gland atrophy, abundant periductal plasma cells, few eosinophils, phlebitis, and lymphoid follicles consistent with CSS. Similar features were seen in the submandibular mass (Fig. 1A). The cervical lymph nodes showed follicular hyperplasia with numerous follicular and interfollicular plasma cells and eosinophils.

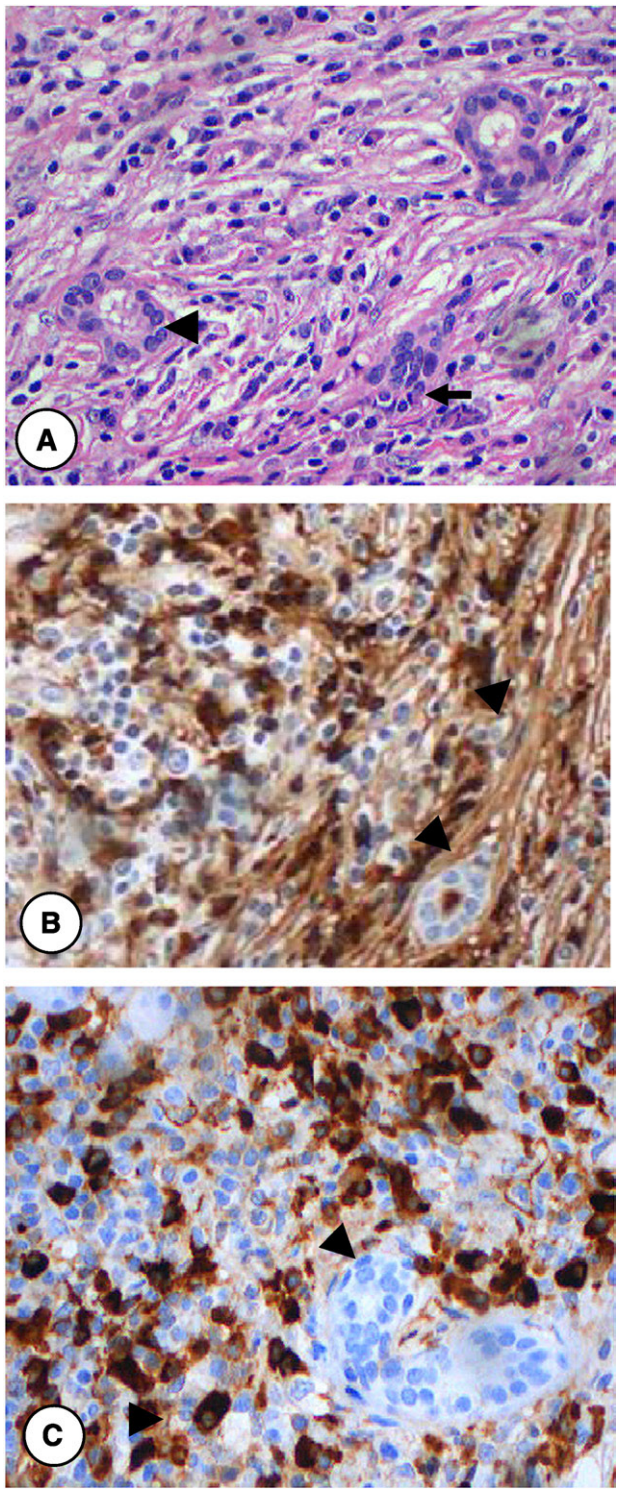

Fig. 1 A, Submandibular gland tissue (hematoxylin and eosin, ×400) with atrophic glands (arrowhead), adjacent fibrosis and lymphoplasmacytic infiltrate (arrow). Immunohistochemical studies (×200) on submandibular gland tissue show positive staining of plasma cells with IgG (B) and IgG4 (C) surrounding the atrophic glands (arrowhead).

Immunohistochemistry performed on the parotid gland carcinoma showed positive expression of epithelial membrane antigen and high-molecular-weight cytokeratin and no

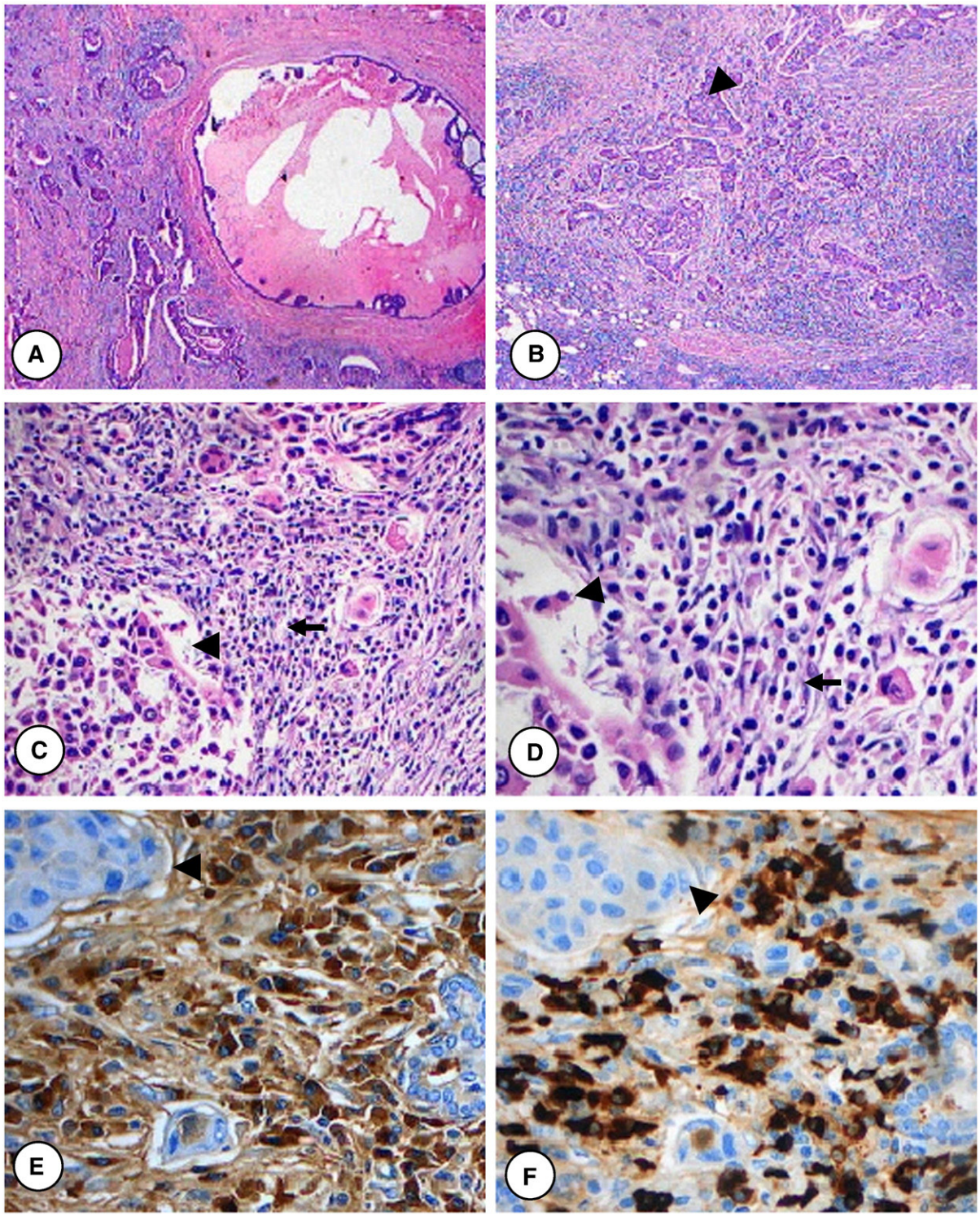

Fig. 2 A, Parotid gland tissue (hematoxylin and eosin, ×20) with salivary duct carcinoma showing ductal carcinoma in situ (DCIS) with micropapillary features. B, Parotid gland tissue (hematoxylin and eosin, ×40) with salivary duct carcinoma (arrowhead) adjacent normal salivary gland. C, Parotid gland tissue (hematoxylin and eosin, ×200) with salivary duct carcinoma (arrowhead) surrounded by fibrosis and lymphoplasmacytic infiltrate (arrow). D, Parotid gland tissue (hematoxylin and eosin, ×400) with salivary duct carcinoma (arrowhead) surrounded by fibrosis and lymphoplasmacytic infiltrate (arrow). E, Immunohistochemical studies (×400) show IgG-positive plasma cells adjacent salivary duct carcinoma (arrowhead) in the parotid gland. F, Immunohistochemical studies (×400) show IgG4-positive plasma cells adjacent salivary duct carcinoma (arrowhead) in the parotid gland.

expression of carcinoembryonic antigen in keeping with salivary duct carcinoma. An immunopanel performed on the submandibular mass showed that there was a mixed population of lymphocytes that expressed T-cell marker, CD3, and B-cell marker, CD20. Small lymphoid follicles with a predominance of B cells were seen. There were focal germinal centers that were BCL2-negative. κ and λ were equally positive in the reactive and sclerotic areas. The Congo red for amyloid was negative in the submandibular and parotid gland samples. The plasma cells in the parotid gland (Fig. 2E and F) carcinomatous and noncarcinomatous areas, submandibular gland (Fig. 1B and C), and cervical lymph nodes (Fig. 3A and B) were strongly immunoreactive for IgG (Invitrogen, Zymed, CA) and IgG4 (Invitrogen, Zymed, CA) with densities of more than 100 per high-power field (/hpf). The IgG4-positive plasma cells accounted for more than 40% of IgG-positive plasma cells.

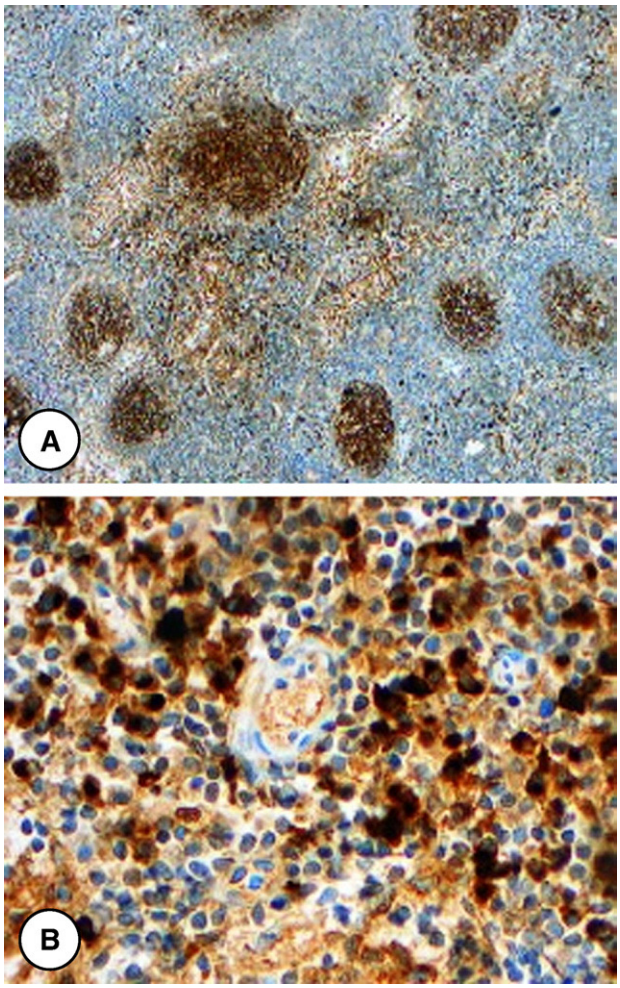

Fig. 3 A, Immunohistochemical studies on cervical lymph node (×40) show follicular hyperplasia with abundant IgG4-positive plasma cells within the follicular centers and interfollicular areas. B, Immunohistochemical studies (×400) show IgG4-positive plasma cells (>100/hpf) in the interfollicular areas of the cervical lymph node.

4. Discussion

The term *hyperIgG4 disease* or IgG4-related sclerosing disease/autoimmune disease was coined in the last decade for an entity that has distinct features and numerous manifestations. It first came to light in 2001 when Hamano et al [3] showed raised serum concentrations of IgG4 in autoimmune pancreatitis (AIP), which lowered with corticosteroid therapy. Hamano et al [9] later found that 3 of 22 patients with AIP had retroperitoneal fibrosis, with abundant IgG4-positive plasma cells. A subsequent case report [10] demonstrated retroperitoneal fibrosis, mediastinal fibrosis, and raised IgG4 levels without AIP highlighting the spectrum of IgG4 disease. Within the English literature, similar cases involving different sites have been reported including inflammatory abdominal aortic aneurysm, inflammatory pseudotumors of the lung and breast, CSS, chronic sclerosing cholangitis, and dacryoadenitis. The age-group of hyperIgG4 disease patients is typically between 50 and 70 years with men affected 2 to 3 times more commonly than women [1].

IgG4 is the least abundant of the IgG subclasses, accounting for less than 6% of the total IgG in the normal population. In bronchial asthma, IgE participates in the reaction to allergens, whereas IgG4 becomes prominent only late during chronic antigenic stimulation. Therefore, IgG4-producing plasma cells might behave as memory cells in allergic patients. Hamano et al [3] found only 20% of their IgG4-related AIP patients had raised serum IgE levels; hence, it was unlikely for an exogenous antigen to be responsible for the rise in IgG4. They also found that the patients with sclerosing pancreatitis had elevated serum concentrations of immune complexes containing IgG4, and the concentrations decreased with steroid therapy, suggesting that the immune complexes are closely related to the pathogenesis of this disease. Deshpande et al [5] identified electron dense immune deposits within pancreas and kidney for 7 of 9 cases of AIP. This was confirmed on tissue immunohistochemistry as IgG4 deposits within the renal tubular basement membranes, providing further proof of both the systemic and the autoimmune nature of this disease. Kitagawa et al [8] in a review of CSS speculated that an increased IgG4 response to antigenic materials around ducts of salivary glands and pancreas may play a key step in the pathogenesis. In a recent study [7] of the dynamics involved in the fibrogenic process in AIP, no difference was found in expression of profibrotic cytokines and their respective receptors between IgG4-positive and negative AIP cases. This study [7] showed that IgG4 expression is not directly implicated in the profibrotic mechanisms.

Malignancy in a background of hyperIgG4 disease has been described in the pancreas. The most recent [12] is of pancreatic carcinoma with background IgG4-related autoimmune pancreatitis. The other cases were of pancreatic carcinoma [13] with IgG4-related regional lymphadenopathy but no evidence of autoimmune pancreatitis and pancreatic

carcinoma [14], diagnosed on pancreatic duct brushings, with elevated IgG4 levels. In addition, Cheuk et al [15] described 3 cases of adnexal lymphoma arising in IgG4-related chronic sclerosing dacryoadenitis; two of the patients had biopsy-proven IgG4-related chronic sclerosing dacryoadenitis before presenting with lymphoma. The third case had increased IgG4-positive plasma cells in a prior nasopharyngeal biopsy. In their report, Cheuk et al [15] also described 3 further cases of ocular adnexal extranodal marginal zone B-cell lymphoma that showed sclerosing inflammation in the background and numerous IgG4-positive plasma cells.

Chronic sclerosing sialadenitis has been referred to as *Kuttner's tumor* because of its presentation as a firm swelling of the salivary gland that is difficult to differentiate from a neoplasm. Our case represents the first epithelial neoplasm documented with background CSS-related IgG4 disease.

Lymphadenopathy [2,8,11,13] has been reported in several case reports of IgG4-related autoimmune disease. These can occur as regional or nonregional lymph node involvement of organs affected by hyperIgG4 disease. Cheuk et al [11] also identified a group with lymphadenopathy and raised IgG4 levels with no organ involved and suggested a lymphadenopathic form of this disease. The cases [11] with primary lymphadenopathy usually have multiple lymph node involvement, commonly of the mediastinal, intraabdominal, and axillary groups, and the involved lymph nodes are not usually large. In our patient, cervical lymphadenopathy was noted at surgery, whereas mediastinal lymphadenopathy was noted in a postoperative computer tomographic scan.

In their study, Hamano et al [3] measured serum IgG4 levels in 20 patients with AIP and 70 patients with pancreatic carcinoma and found that none of the carcinoma cases had elevated IgG4. Serum IgG4 is elevated in atopic dermatitis, helminthic diseases, pemphigus vulgaris, and pemphigus folliaceus. Hamano et al [3] reported that serum total IgG concentrations were slightly higher in the patients with sclerosing pancreatitis, but there was considerable overlap with pancreatic cancer, primary biliary cirrhosis, and Sjogren's syndrome. Some case reports [2] noted normal serum IgG levels. Some patients have peripheral eosinophilia [8] or elevated IgE levels [4], whereas others have elevated erythrocyte sedimentation rate and C-reactive protein [1] levels.

Histologic sections from the salivary gland of hyperIgG4 disease-related CSS shows diffuse lymphoplasmacytic infiltration, irregular fibrosis, and obliterative phlebitis with abundant IgG4 plasma cells. Interestingly, the lymphoplasmacytic infiltration can be seen scattered in non-CSS areas of affected salivary gland. Eosinophilic infiltration can be conspicuous with atrophy or destruction of the salivary glandular lobules and lymphoid follicles with germinal centers. Cheuk et al [11] in a review of lymphadenopathy related to hyperIgG4 disease noted that the morphology of regional and nonregional lymph nodes can be broadly divided into 3 patterns characterized by Castleman disease-like, follicular hyperplasia, and interfollicular expansion.

IgG4 tissue immunoperoxidase stain provides solid adjunctive evidence of hyperIgG4 disease. Kojima et al [6] found that IgG4 plasma cells counts of more than 20/hpf is highly specific for the diagnosis of AIP. However, Deshpande et al [5], in a systematic study of tissue immunohistochemical staining for IgG4, commented that overlaps between AIP, chronic pancreatitis, and adenocarcinoma preclude the use of immunolabeling as a diagnostic tool, particularly when evaluating pancreatic biopsy specimens. In a recent study [11], large numbers (>100/hpf) of IgG4-positive plasma cells may be found in reactive lymph nodes not associated with IgG4 systemic disease, but these would account for less than 30% of all IgG plasma cells. In contrast, in IgG4-related lymphadenopathy, IgG4-positive plasma cells were found in extreme numbers and always accounted for more than 40% of IgG-positive cells.

HyperIgG4 disease/IgG4-related sclerosing disease/autoimmune disease is a clinically distinct condition that can be diagnosed on serologic, histologic, and clinical response to steroids. The association of malignancy in contiguity with this disease is documented with this case report. This allows for speculation of progression from longstanding IgG4-related autoimmune disease to malignancy. However, the possibility of unrelated dual pathologic examination cannot be ruled out. This case emphasizes caution in interpretation of masses with raised serum IgG4 levels and histologic characteristic of hyperIg4 disease, as the differential diagnosis includes malignancy.

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