ORIGINAL ARTICLE

IgG4 related sclerosing sialadenitis- a retrospective analysis

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Abstract

Background: IgG4 related disease rarely affects the salivary glands and clinically is often confused with salivary gland malignancy. Method: This is a retrospective study comprising 137 cases of chronic sialadenitis diagnosed in a histopathology department over 4 years. The morphology was assessed by reviewing the histology slides and the incidence of IgG4 related sclerosing sialadenitis was calculated. IgG and IgG4 immunohistochemistry was performed and mean IgG4 count/hpf and IgG4/IgG ratio were determined. Clinical findings were obtained from medical records. Results: Of the 137 cases reviewed, 3 cases showed diagnostic histological features of IgG4 related sialadenitis, these being: a prominent lymphoplasmacytic infiltrate, lobular fibrosis, acinar atrophy, obliterative phlebitis and mean IgG4 count of 86/hpf with mean IgG4/IgG ratio 65%. No further disease was documented at follow-up which ranged from 24 to 36 months. Conclusion: The incidence of IgG4 related sialadenitis in the present study is 2%, indicating that it is a rare condition. Since there is no non-invasive diagnostic modality, either core biopsy or surgical excision is required for definitive histological diagnosis.

Key words: sialadenitis, IgG4, sclerosis

INTRODUCTION

Chronic sclerosing sialadenitis is a fibro-inflammatory disease of the salivary glands that presents with a firm swelling of the gland and often mimics a neoplasm clinically.1 This lesion shows a predilection for the submandibular gland, although parotid gland involvement has also been described.2 The disease was originally described by H. Kuttner in 1896. It occurs typically in middle-aged to elderly persons with a slight male predominance. Recent evidence suggests that Kuttner tumour may be a type of disorder characterized by IgG4-related disease.3,4 IgG4-related disease has only been established as an entity in this century, but there is already an extensive literature, documenting increasing numbers of cases of IgG4-related sialadenitis.5,7 However, the incidence of IgG4-related sialadenitis among cases of chronic sialadenitis is unknown. We performed a retrospective analysis of chronic sialadenitis to assess incidence and morphology of this disease.

MATERIALS AND METHODS

The study included 137 cases of chronic sialadenitis diagnosed in the histopathology department of an academic tertiary cancer centre over a period of 4 years from 01/01/2010 to 31/01/2014. The histopathology Winpath computer database was searched for cases of chronic sialadenitis. All H&E stained slides and IgG4 immunohistochemistry stained slides (wherever performed) were reviewed to assess for the presence of an increased number of IgG4 positive plasma cells in a background of inflammation, fibrosis and obliterative phlebitis. Relevant histochemistry (Elastic-Van Gieson stain) and immunohistochemistry was performed in selected cases to confirm the diagnosis. CD138, IgG4 and IgG immunostains were performed using a Ventana BenchMark Ultra Autostainer in all suspected sclerosing sialadenitis cases. IgG4 and IgG stains were also performed in 95 chronic non-specific sialadenitis cases and 6 lymphoepithelial sialadenitis (LESA) cases for comparison. The numbers of plasma cells stained for IgG and IgG4 in the area of maximum density of inflammation were counted in three high power fields of an Olympus microscope. The mean IgG4 count and IgG4: IgG ratio were recorded. The criteria mentioned in the 2012 consensus statement on the pathology of IgG4-related disease were adopted for diagnosis.8 Clinical
features and radiological findings were noted from medical records and the hospital clinical data recording system. Age, gender, presenting complaints, clinical symptoms and site of biopsy/ excision were noted. The incidence of IgG4 related sialadenitis was calculated.

RESULTS

The 137 cases included 95 major salivary gland resections and 42 minor gland biopsies. Three of these 137 cases showed characteristic histological features. The lesions presented as discrete firm fibrotic masses within the submandibular salivary gland on macroscopical examination. There was dense lymphoplasmacytic infiltrate of lobules with maintained lobular architecture (Fig. 1A). Lymphoid follicles were also noted against a fibrotic stroma (Fig. 1B). All three cases showed variable degrees of fibrosis characterized by a highly cellular proliferate composed of plump fibroblasts, lymphocytes and mature plasma cells (Figs. 1C & 1D). Two of these 3 cases showed characteristic storiform pattern. Marked acinar atrophy was also noted (Fig. 1E). Mild to moderate tissue eosinophilia was present in two cases. Perineural collections of plasma cells were also seen in 2 cases (Fig. 1F). Phlebitis was present in all two cases which were confirmed by Elastic-Van Gieson stain (Figs. 2A & 2B). Lymphoepithelial lesions or presence of intraductal sialoliths were not identified in any of these 3 cases. The number of IgG4 positive plasma cells ranged from 55 to 114 (mean 86) per high power field and IgG4 to IgG ratio ranged from 55 to 88% (mean 65%) in our cases (Figs 2C & 2D).

All three cases were males with age >65yrs and presented as painless nodular enlargement of submandibular gland. Extra-salivary glandular lesion such as sclerosing cholangitis, retroperitoneal fibrosis or sclerosing pancreatitis was not seen.

Based on these characteristic histological features and IgG4 counts of >50/hpf and IgG4:IgG ratios of >50%, the diagnosis on IgG4 related sclerosing sialadenitis was made in 3 of 137 cases in this study (with an incidence of ~2%). No further disease was documented at follow-up ranging for 24-36 months.

The absence of prominent lymphoepithelial lesions and of sialolithiasis assisted to differentiate IgG4 related sialadenitis from nonspecific chronic sialadenitis and lymphoepithelial sialadenitis. The 95 cases of non-specific chronic sialadenitis showed variable degrees of fibrosis and chronic inflammation, and there was not a significant number of plasma cells and the average number of IgG4 positive plasma cells was <5% (range 3-6%). The 6 cases of lymphoepithelial sialadenitis (LESA) showed prominent lymphoepithelial lesions with formation of lymphoid follicles and again the number of IgG4 positive plasma cells was <5%.

DISCUSSION

IgG4–related disease (IgG4-RD) is an increasingly recognized disorder of unknown aetiology characterised by specific histological, serological and clinical features. Some data from literature support an immune-mediated condition that can affect almost any organ. The cardinal histopathological features of this condition are dense lymphoplasmacytic infiltrate with IgG4 positive plasma cells, lymphocytes, variable degree of storiform fibrosis, mild to moderate eosinophilia and obliterative phlebitis. Also, elevated serum concentrations of IgG4 are found in 60-70% of patients with IgG4-RD. The common clinical features include tumour-like swelling of involved organs, type 1 autoimmune pancreatitis; but also multiple organs can be affected in 60-90% of patients with IgG4-RD. Some of other IgG4-RD associated disorders are sclerosing sialadenitis, idiopathic retroperitoneal fibrosis, inflammatory orbital pseudotumour, interstitial pneumonia and kidney disease.

The disorder that was identified by Kuttner in 1896 differs from nonspecific chronic sialadenitis in salivary gland as it commonly involves the submandibular gland, clinically presents as hard tumour-like mass and the pathology shows prominent lymphoplasmacytic infiltrate accompanied by progressive fibrosis. However, there are very few studies, mostly from the South Asian countries which examined the relationship between chronic sclerosing sialadenitis and IgG4-RD. Our study conducted on a western population found 3 cases of sclerosing sialadenitis out of 137 cases of chronic sialadenitis with the above clinical and pathological features. Most often IgG4-RD occurs in middle-aged and older men, although studies of IgG4 related sialadenitis have shown more equal sex distribution. In our study all three cases were males with age >65yrs and presented as painless nodular enlargement of unilateral submandibular gland. In one patient...
FIG. 1: Characteristic histological features of chronic sclerosing sialadenitis. A: Discrete fibrotic mass with lobular fibrosis and prominent lymphoplasmacytic infiltrate (H & E 40X). B: Lymphoid follicles against dense fibrotic stroma (H & E 40X). C & D: Prominent lymphoplasmacytic infiltrate associated with destruction and atrophy of salivary gland tissue (H & E 100X). E: Higher magnification showing dense infiltrate of mature plasma cells and lymphoid cells, but no lymphoepithelial lesions (H & E 400X). F: Prominent perineural lymphoplasmacytic infiltrate (H & E 400X).
FIG. 2: A: Obliterative phlebitis showing marked inflammatory cell infiltrate and fibrin deposition of vessel wall (H & E 200X). B: Elastica- Van Gieson stain demonstrating the destruction of internal elastic lamina of the vessel wall (200X). C: IgG immunostaining highlighting the plasma cells (200X). D: A good proportion of plasma cells showing strong expression of IgG4 (200X).

after two years another mass was found in other submandibular gland, but the patient refused further investigation. Histopathological findings were characteristic in all three cases and these appearances were similar to the inflammatory proliferation seen in cases of autoimmune pancreatitis. On the basis of unique histological appearance of chronic sclerosing sialadenitis and the presence of increased numbers of IgG4 positive plasma cells in our study as well as two previous studies in the literature, would justify replacing the “Kuttner tumour” with the term “IgG4 related sclerosing sialadenitis”. In our study on further follow up of 24-36 months, none of the cases showed other manifestations of IgG4 related systemic disease.

IgG4- related chronic sclerosing sialadenitis patients may show an elevated serum IgG4 levels. Serum IgG4 levels were not analysed pre and post operatively in all three cases in our study. However, less than 40% of patients with IgG4-RD have normal serum IgG4 concentrations despite the presence of classic histopathological changes in tissue.12

It is important to differentiate IgG4 related sialadenitis from chronic nonspecific sialadenitis based on histological appearances. Chronic nonspecific sialadenitis is usually due to sialolithiasis or other conditions such as smoking. Histologically it is characterized by a bland acellular interlobular fibrosis and an inflammatory infiltrate which contains scanty lymphocytes with few lymphoid follicles. In contrast, IgG4 related sialadenitis shows cellular fibrosis with storiform pattern and it may show follicular hyperplasia with large geographic lymphoid follicles.1 Approximately more than half of cases of chronic nonspecific sialadenitis in our study showed evidence of sialolithiasis including marked ductal dilatation with mucosal denudation or squamous metaplasia. However, intraglandular stones or ductal epithelial changes were not identified in cases diagnosed as IgG4 related sclerosing sialadenitis in our study.

Also, chronic sclerosing sialadenitis is distinguishable from other inflammatory diseases
in the salivary gland such as lymphoepithelial sialadenitis (LESA) and Sjogren syndrome. LESA is a histopathological disease process that usually manifests in the parotid glands in about 90% of cases and, less frequently, the sub-mandibular glands. Also it commonly occurs bilaterally. Histologically LESA is characterized by lymphocytic infiltration of the gland, parenchymal atrophy and foci of epithelial proliferation with lymphocytic epitheliotropism (lymphoepithelial lesion). However, LESA does not show interlobular cellular fibrosis or increase IgG4 positive plasma cells. Sjogren’s syndrome (SS) is an autoimmune disease complex that involves the lacrimal and salivary glands commonly involving the parotid glands. SS typically shows the histopathological features of LESA; however, not all patients with histopathological features of LESA have the clinical and laboratory signs of SS such as anti-SSA, anti-SSB, rheumatoid factor, and salivary duct antibody.

It should be emphasized that just the presence of high levels of IgG4 positive plasma cells in absence of classical histopathological features should not be considered as diagnostic of IgG4 related sialadenitis. Harrison JD and Rodriguez-Justo M recently described 3 cases in their study that had IgG4 count >50/hpf; however, these cells were part of a non-specific chronic inflammatory infiltrate associated with ducts that had contained sialoliths. Steroids are well established in the treatment for sclerosing pancreatitis and similarly, in the literature, immunosuppressive therapy has been shown to be an effective treatment in IgG4 related sialadenitis. In our study once the lesions were removed patients acquired complete recovery therefore further treatment was not given. Recently, Witte and Schulze-Koops suggested that a core biopsy from a major salivary gland may be helpful in definitive histological diagnosis and could justify prolonged steroid therapy as a mode of treatment. In summary, this study shows that IgG4-related sclerosing sialadenitis is a rare (incidence only 2% in our study) but definite entity and strict histopathological criteria should be used for its diagnosis. Since there is no non-invasive diagnostic modality, core biopsy or surgical excision is required for a definitive histological diagnosis.

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REFERENCES