Review

IgG4-related Mikulicz's disease is a multi-organ lymphoproliferative disease distinct from Sjögren's syndrome: a Caucasian patient and literature review

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Received on July 6, 2012; accepted in revised form on September 6, 2012.

Clin Exp Rheumatol 2013; 31: 289-294.

Key words: Mikulicz's disease, IgG4, IgG4-related disease, submandibular gland, PET

Competing interests: none declared.

ABSTRACT

Objectives. *This paper aims to report a case of IgG4-related Mikulicz's disease with a systematic review.*

Methods. *The relevant English literature was searched using the keywords "Mikulicz's disease" and "IgG4" Original and review articles were reviewed, and the clinical scenarios were exemplified with a case report.*

Results. *A 49-year-old Caucasian man presented with axillary lymphadenopathy and bilateral parotid/submandibular enlargement. A chest computerised tomography showed mediastinal lymphadenopathy, with low metabolic activity on the position emission tomography. A histopathological study showed an IgG4/IgG ratio of 75% in the plasma cells of the submandibular glands, associated with high levels of total serum IgG and IgG4. He had dry mouth, but minor salivary gland biopsy was negative without xerophthalmia. He had nasal obstruction and dyspnea, notably with supine position/cervical rotation, which substantially improved with glucocorticoid treatment. He had newly diagnosed diabetes mellitus with hyperlipasaemia and diffuse pancreatic swelling supportive of autoimmune pancreatitis.*

Conclusion. *Our case report supports the literature that there are similarities between IgG4-related Mikulicz's disease and Sjögren's syndrome, but the differences are significant. IgG4-related Mikulicz's disease is a multi-organ lymphoproliferative disease distinct from Sjögren's syndrome.*

Introduction

Immunoglobulin G4(IgG4)-related disease is a lymphoproliferative disorder associated with hyper IgG4 gammaglobulinaemia and an IgG4 producing plasma cell expansion in affected organs with fibrotic or sclerotic changes (1). This is a broad spectrum disease which may involve multiple organ sites, with numerous designated names previously for the disease, but recommendations for a unified nomenclature have been recently proposed (2). Cases previously classified as Mikulicz disease (MD) have been recently associated with elevated serum and tissue IgG4 as well (3). The overwhelming majority of the publications concerning IgG4-related MD are from Japanese studies, and there are seldom case reports of this disease from the United States and Europe. Herein, this disease is exemplified with a Caucasian patient who underwent a thorough workup, including positron emission tomography (PET) scan in the context of the diagnosis, pathogenesis, and prognosis.

Patients and methods

PubMed was used for the literature search from 1928 onward. The search was limited to publications in English and the keywords used were as follows: ("immunoglobulin g" [MeSH Terms] or "immunoglobulin g" [All Fields] or "igg4" [All Fields]) and ("mikulicz' disease" [MeSH Terms] or ("mikulicz'" [All Fields] and "disease" [All Fields]) or "mikulicz' disease" [All Fields] or ("mikulicz's" [All Fields] and "disease" [All Fields]) or "mikulicz's disease" [All Fields]). The computerised search was completed with a manual search of pertinent reference lists from the relevant articles retrieved. A PRISMA statement was followed to detail the data gathering process (Fig. 1). The immunohistochemistry staining of the IgG4 in the tissue was performed in the Department of Anatomic Pathology at the Cleveland Clinic, and IgG4/total

IgG ratio was computed per the standard set forth in the literature (4). The PET/CT scan was performed 40 minutes after intravenous injection of 10 mCi F-18 Fluorodeoxyglucose (FDG). The images were acquired from the skull base to the mid thigh.

Results

Case report

A 49-year-old white man presented with a history of painless left axillary lymph node enlargement 2 years ago, which was surgically biopsied without evidence of malignancy. He later found asymptomatic bilateral submandibular enlargement described as marble-like feeling upon swallowing. He also had sinusitis-like symptoms consisting of stuffy/clogged nose and mild dyspnea without cough, which worsened with a supine position or cervical rotations,but significantly improved with an upright position. He had scant whitish nasal discharges but without sneezing or runny nose. An evaluation of the ear, nose and throat with computerised tomography (CT) scan of the sinuses was only positive for mild left maxillary sinusitis. He received intramuscular injections of methylprednisolone 40 mg three times over a 2-month period with significant improvement of the sinusitis-like symptoms. He later felt thirsty and was diagnosed with type II diabetes mellitus with glycosolated haemoglobin of 8.5% requiring insulin treatment. Review of systems was positive for fatigue and mild weight loss, but without fever, night sweats, rash, arthralgia, dry eyes/mouth, nausea, vomiting, abdominal pain or diarrhea.He was allergic to penicillin and sulfa drugs, and was taking levothyroxine for hypothyroidism. On physical exam, his body mass index was 30.7 kg/m^2, and there was bilateral nontender but firm submandibular gland and diffuse parotid gland enlargement (Fig. 2A). Otherwise, the physical exam was unremarkable. Ophthalmic exam was negative for Schirmer test and Rose Bengal staining of the eye.

Laboratory results

Complete blood count and comprehensive metabolic panel were normal except for elevated glucose. Serum lipase was 177 (12–70 Units/L) and amylase was normal. Antinuclear antibodies (ANA) and anti-extractable nuclear antigen antibodies were negative, rheumatoid factor was 27 (normal <20 IU/ml). Total serum IgG was 1808 (normal 717–1411 mg/dl), IgG1 936 (normal 456–1110 mg/dl), IgG2 596 (normal125–630 mg/dl), IgG3 118(normal 25–113 mg/dl), and IgG4 613 (normal 11–112 mg/dl) with IgG4/IgG ratio of 0.34 (0.05–0.079). Serum IgA was 235

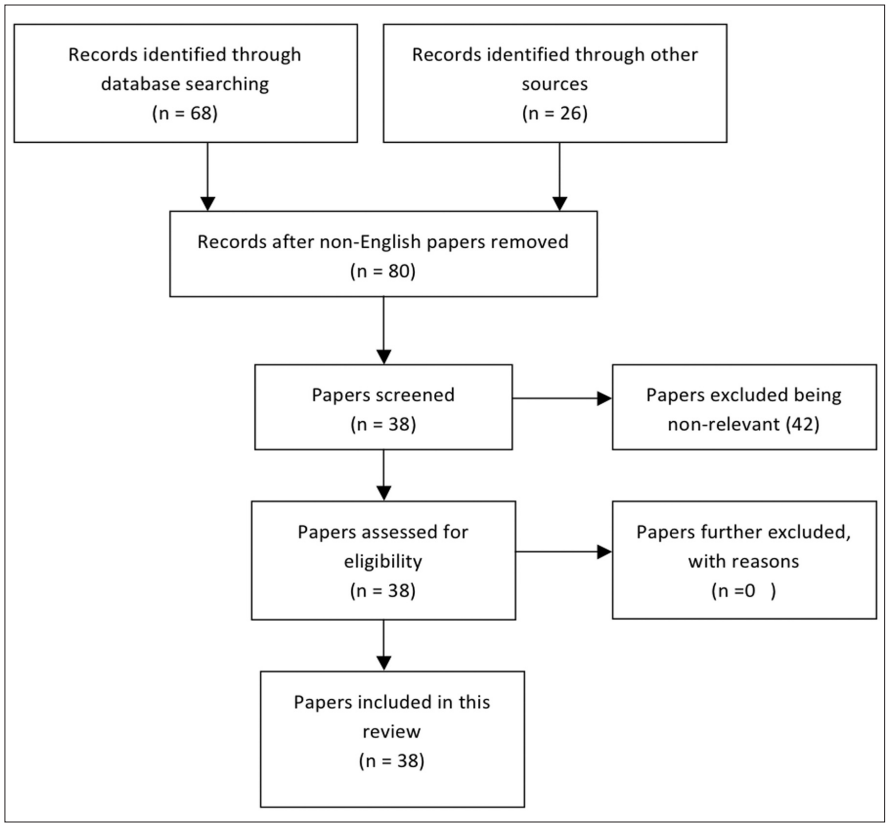

Fig. 1. PRISMA Flowchart depicting the articles retrieved, excluded, and selected.

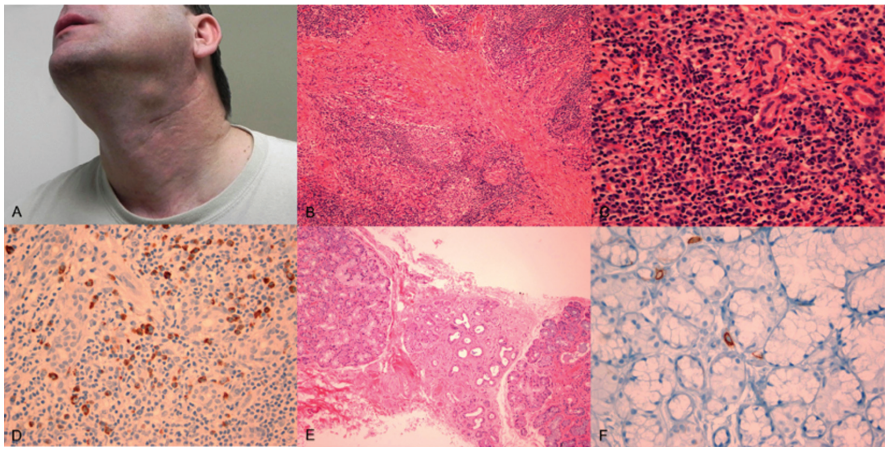

Fig. 2. Submandibular and parotid gland enlargement in **A**; Submandibular gland demonstrating lymphoplamacytic infiltration with germinal center formation and fibrosis, forming storiform fibrosis, haematoxylin and eosin (H&E) stains, 100x in **B**; Residual submandibular ducts with a dense infiltrate of chronic inflammation, predominately lymphocytes and plasma cells, H&E stains, 400x in **C**; Submandibular gland with a marked increase in IgG4-positive plasma cells, IgG4 immunohistochemistry, 400x in **D**; Minor salivary gland biopsy with focal atrophy but no significant inflammatory infiltrates, H&E stains, 100x in **E**; Minor salivary gland with occasional plasma cells, CD138 immunohistochemistry, 400x in **F**.

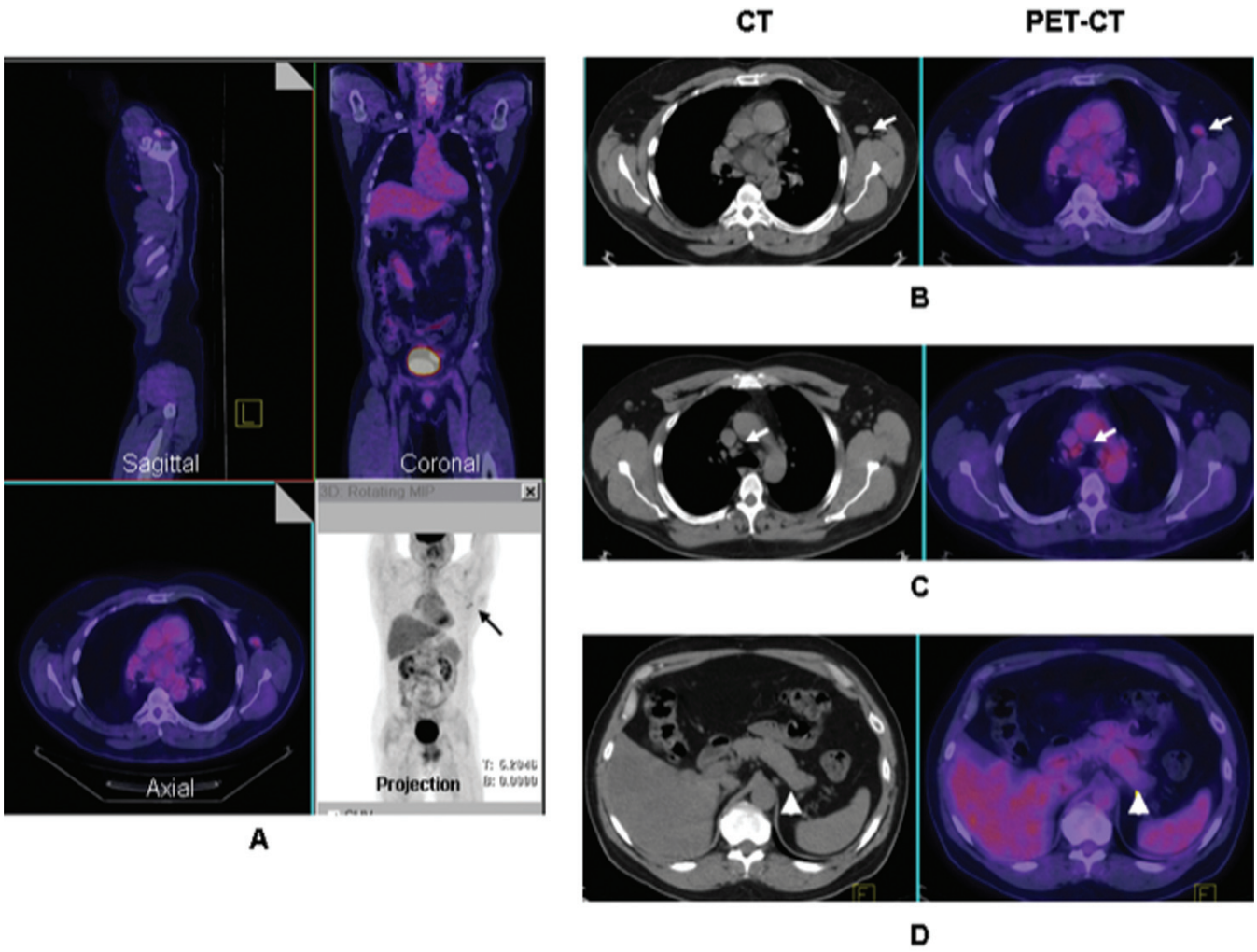

Fig. 3. PET/CT 3D fusion and projection images showing enlarged left axillary lymph nodes (black arrow) in **A**; Axial and fused PET/CT images showing enlarged left axillary lymph nodes in **B**; mediastinal lymphadenopathy in **C**; and diffuse pancreatic swelling in **D**.

(normal 78–391 mg/dl), IgM 50 (normal 53–334 mg/dl), and IgE 124 (normal<114 ku/L). Serum Kappa was 1100 (normal 534–1267 mg/dl) and Lambda 1120 (normal 253–653 mg/dl) with a Kappa/Lambda ratio of 0.98 (normal 1–3). Serum M protein was absent, and CH50 and complement 3/4 were normal. Serum cytomegalovirus IgG and IgM were negative; Epstein-Barr virus IgG was more than 8 AU with negative IgM, early antigen and nuclear antigen; toxoplasmosis IgM and IgG were negative. Blood CD3, CD3CD4, CD3CD8, CD4/CD8, CD19, and natural killer cells all were within normal limits.

Imaging studies

An CT scan of the chest, abdomen, and pelvis showed slightly enlarged bilateral hilar/subcarinal lymph nodes and diffuse pancreatic swelling (Fig. 3). The PET/CT scan showed a handful of left axillary lymph nodes (Fig. 3) exhibiting mild level of the 18-FDG uptake (the standardised uptake value up to 2.3) similar to that demonstrated 2 years ago. There were some borderline enlarged mediastinal lymph nodes seen in the left prevascular space and precarinal region. None of these particular lymph nodes exhibited a significant increase in metabolic activity. The FDG uptake in the rest of the body regions was unremarkable.

Histopathology

A submandibular gland biopsy demonstrated massive lymphoplasmacytic infiltration with lymphoid aggregates and fibrosis, forming storiform fibrosis (Fig. 2B). The stroma was extensively infiltrated by mixed chronic inflammation composed mainly of lymphocytes and plasma cells (Fig. 2B-2C). These characteristic pathologic findings favoured chronic sclerosing sialoadenitis (Fig. 2B). There was extensive IgG4 immunohistochemical reactivity in the tissue plasma cells with an IgG4/IgG ratio of 75% (Fig. 2D). Lymphoepithelial lesions were not identified. Flow cytometry analysis showed no evidence of B-cell or T-cell lymphoma. Immunophenotypic analysis showed B cells (47% of total) appeared polytypic and T cells (50% of total) showed no pan-T-cell antigenic deletion with an CD4/CD8 ratio of 1.5/1. The left axillary lymph node excisional biopsy showed reactive follicular hyperplasia with focal progressive transformation of germinal centres but without evidence of lymphoma. A minor salivary gland tissue biopsy showed only focal atrophy without significant inflammatory infil-

trates consistent with a Chisholm-Mason score of 0 (Fig. 2E). Immunohistochemical stains for CD138, IgG, and IgG4 were performed with only rare plasma cells noted (Fig. 2F).

Literature review

Historical data of MD before the era of the hyper IgG4-related disease

In 1888, Johann von Mikulicz-Radecki, a surgeon who was born in Cernowitz, then Austria, but now Poland (5), first described a patient with symmetrical enlargement of the lacrimal and salivary glands, with the glandular tissue being entirely replaced by lymphoid tissue. This process, however, apparently was not a part of a generalised disease of lymphoid tissue. Subsequently, Smith and Bump (6) summarised approximately 100 cases available as of 1928 and concluded that MD was essentially a disease of the lymphoid tissue of the lacrimal and salivary glands with secondary destruction of the parenchyma. Lymph nodes in the gut and spleen could also be affected. A follow-up of some patients with the disease for up to 12 years did not reveal any malignancies. The authors, therefore, noted that this lymphoid tissue, for the most part solitary nodes in hyperplasia of the lacrimal and salivary glands and about the walls of the gland ducts, underwent or was subject to diseases quite like those of lymphoid tissue elsewhere in the body. It carried a wholly different prognosis than leukaemia or Hodgkin's lymphoma (6, 7). In 1953, Morgan and Castleman had studied 18 MD patients and proposed that the histological findings in MD and Sjögren syndrome (SS) were similar, and MD could be part of SS (8). Historically, there was some debate over the use of the terminology MD *versus* Mikulicz's syndrome, because there were a few case reports where haematological malignancies, such as mantle cell lymphoma, non-Hodgkin's lymphoma, and lymphosarcoma, could present with MD-like pictures (9-11). To avoid the confusion, it was later recommended in the literature to retain MD and avoid the term Mikulicz's syndrome, as MD rarely developed into lymphoma or leukaemia (12, 13).

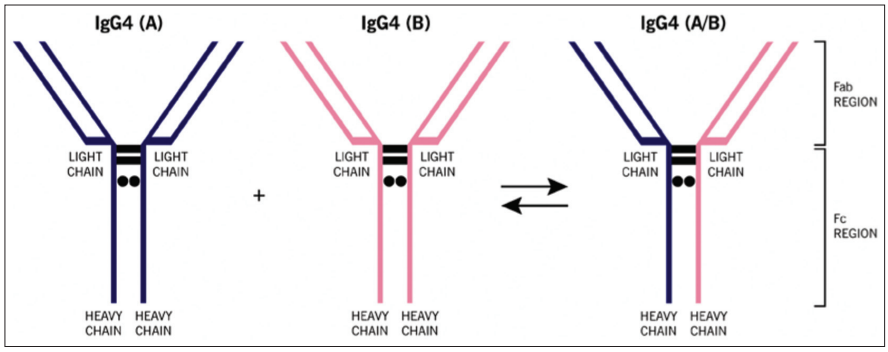

Fig. 4. A heavy chain and light chain pair (half-molecule) of one IgG4 molecule exchanges with that of another IgG4 molecule to form the IgG4 molecule, which may thereby acquire two distinct Fab arms and become bispecific. The Fc structure remains essentially unchanged.

The current data of MD after the discovery of the hyper IgG4-related disease

Since the first report of patients with elevated serum IgG4 in sclerosing pancreatitis by Hamano *et al*. in 2001 (14), various systemic disorders associated with hyper IgG4 with many different designated disease names have been reported (1). Among them, MD has been reported by Yamamoto *et al*. to be associated with elevated IgG4 in 2004 (15). MD is one of the multi-organ lymphoproliferative diseases (MOLPD) and is considered to differ from SS (16, 17). The clinical, laboratory, and pathological manifestations of IgG4-related MOLPD *versus* primary SS are distinct (18). Of the 64 patients reported, women/men were 33/31 in IgG4+MOLPD *versus* 29/2 in SS. Despite similarities in the distribution of organ involvement, there were considerable clinical and pathological differences in the frequency of the organ involvement between IgG4+MOLPD and SS. The frequency of xerostomia, xerophthalmia, arthralgia, rheumatoid factor, ANA, and anti-SSA/anti-SSB antibodies was significantly lower in IgG4+MOLPD (18).

The diagnosis of IgG4+MOLPD is defined as having both raised serum IgG4 level >135 mg/dl and histopathological feature including lymphocyte and IgG4+ plasma cell infiltration >50% with typical fibrosis or sclerosis in the tissue (18). Additionally, the diagnosis of IgG4-related MD is met if there are visual confirmation of symmetrical and persistent swelling in more than two lacrimal and major salivary glands; prominent mononuclear infiltration of lacrimal and salivary glands; and exclusion of other diseases that present with glandular swelling, such as sarcoidosis and lymphoproliferative disease (17).

The clinical manifestations of our patient were characterised by bilateral submandibular and parotid gland enlargement, lymphadenopathy in the thorax and periphery, respiratory symptoms, and newly diagnosed diabetes mellitus, with hyperlipasaemia and diffuse pancreatic swelling. There were substantially increased serum IgG4 level and tissue plasma cell IgG4/IgG ratio (75%) but without histopathologic evidence of lymphoma or sarcoidosis. There was a lack of xerophthalmia, xerostomia, ANA, and anti-SSA/SSB antibodies, and minor salivary gland biopsy was negative for SS, though anti-Ro52 antibodies were not specifically tested (19). These features of our patient apparently fulfilled the proposed diagnostic criteria for IgG4 related MD.

The etiopathogenesis of the IgG4-related MD

IgG4 structure is unique and dynamic, as shown in Figure 4 (20). IgG4 makes up 4% of the total IgG level, and its value is important in the diagnosis of IgG4-related disease and in differentiation from rheumatic diseases (21), although IgG4 of low level may also occur in Churg-Strauss syndrome, multi-centric Castleman's disease, eosinophilic disorders, some patients with rheumatoid arthritis, systemic sclerosis, chronic hepatitis, and liver cirrhosis. The levels of IgG subclasses 1, 2, and 3 are significantly higher, whereas IgG4

level is lower in primary SS patients (22), favouring the view that IgG4-related MD is distinct from SS. MD was traditionally thought to represent a benign lymphoproliferative disease with rare malignant transformation. Could IgG4-related MD equally carry a good prognosis? Our answer based upon our case report would be positive, since multiple fused PET/CT scans and tissue biopsies did not support a malignancy. Of note, only one similar case of IgG4-related MD has been studied using a whole body FDG-PET/CT scan, which has been purposed to be a useful tool for detecting systemic involvement in the disease (23). It has been reported that the levels of immunoglobulins, notably IgG subclasses IgE and IgG4, are significantly lower in patients with non-Hodgkin's lymphoma (24). In addition, local occurrence of IgG4-related disease in 10 years after radiotherapies to ocular adnexal extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue has been reported (25). An absence of glomerular IgG4 deposition in patients with membranous nephropathy may indicate the occurrence of malignancy (26). These data suggest that IgG4 level might be protective against malignant diseases. However, a Japanese study of 106 patients with IgG4-related disease found 11 cases of malignancy consisting of lung cancer, colon cancer, and lymphoma. These malignancies were observed at the initial diagnosis of IgG4-related disease and during an average follow-up of 3.1 years (27). With the increasingly evolving expansion of the data of IgG4-related disease in the literature, the clinical significance of IgG4 in the formation and possible resolution of lymphoma *versus* solid cancer should deserve further study.

IgG4 is deficient in its ability to activate complement relative to wild-type IgG1. One of the significant differences between the two molecules is in the hinge region. It is quite possible that the rigid hinge of IgG4 impairs access to the Clq binding site, thus decreasing the effectiveness of the molecule in mounting antimicrobial response (28). Consistent with this view is that our case study suggests that infectious agents such as Epstein-Barr virus, cytomegalovirus, and toxoplasma may not participate in the pathogenesis of the IgG4-MD. It is known that IgG4 is involved in allergic reactions (29) and may be anti-inflammatory or protective in such conditions (20). The bispecific IgG4 molecule is a result of dynamic fab arm exchange that involves the third constant domain, as well as the hinge region. This molecule represents a new type of post-translational modification and serves as a mechanism of anti-inflammatory activity (20). IgG4 has been reportedly driven in part by T helper 2 cytokines that mediate allergic responses and IgE production (30, 31). The annoying nasal symptoms and positional dyspnea, as well as high serum IgE level as in our case, may support the potential role of allergic involvement in the disease. In fact, increased IgE level has been reported in some cases of IgG4-related disease (18). The new onset diabetes mellitus, elevated serum lipase, and diffuse pancreatic swelling with hyper IgG4 level, as in our case, are compatible with the occurrence of autoimmune pancreatitis, which has been reported to associate with an earlier onset, female predominance, and diffuse pancreatic swelling, as well as precedence of gastroenterological events (32). In addition, a case of hyper IgG4-related MD has been reported to complicate with interstitial nephritis (33).

Discussion

IgG4-related disease is a recently recognised condition with pathological features that are consistent across a wide range of organ systems (34). In accordance with the literature, our case is classic supporting the view that IgG4-related MD is an MOLPD distinct from primary SS. IgG4MD can mimic SS (35), and two cases of MOLPD have been recently reported, which were initially suspected of having SS (36, 37). MOLPD is a benign lymphoproliferative disease which carries a good prognosis with little malignant transformation. As reported (38), glucocorticod therapy is effective to manage the IgG4-related MD in improving glandular functions and reducing IgG4 level. The recommended initial dose of prednisone is 30–40 mg daily with a maintenance dose of 5–7.5 mg daily. Our patient was initiated with oral prednisone 30 mg daily and had a good clinical response noted 10 days after starting prednisone; there was a 60% reduction in the enlarged submandibular glands and resolution of dyspnea, and complete resolution of the enlarged glands and normalisation of the serum lipase a month later. The potential therapeutic efficacy of other immunosuppressive drugs has been explored. A B lymphocyte depletion drug, rituximab, is an effective therapy for some cases of IgG4-related diseases (34). Since IgG4-related disease has sclerosing changes, we believe that future study of the potentially contributory role of IgG4 in the formation of fibrosis in the lymphoid tissues and potential malignant transformation would be worthwhile.

Acknowledgements

The authors are thankful to Mr Ken Celebucki and Ms Kathy Miller at the Centre for Medical Art and Photography for their technical assistance in the preparation of the photographs and graphics.

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