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Mikulicz's disease: A new perspective and literature review

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PURPOSE. *To report the clinical and pathophysiologic features of two patients with Mikulicz's disease and to further characterize recommendations for diagnosis and management with a review of the literature.*
METHODS. *Retrospective nonrandomized consecutive case series, Jules Stein Eye Institute, David Geffen School of Medicine at UCLA.*
RESULTS. *Mikulicz's disease is characterized by symmetric lacrimal, parotid, and submandibular gland enlargement with associated lymphocytic infiltrations. The authors noted two cases of Mikulicz's disease. The diagnosis of Mikulicz's disease was based on the following criteria: 1) symmetric and persistent swelling of the lacrimal glands and either or both of the major salivary glands (parotid and submandibular); and 2) the exclusion of other diseases that may mimic this presentation, such as sarcoidosis, viral infection, or lymphoproliferative disorders.*
CONCLUSIONS. *Mikulicz's disease is a condition in which there is bilateral lacrimal and salivary gland swelling that is not associated with other systemic conditions. The condition is self-limiting and most often, the diagnosis is a clinical one. Previously, Mikulicz's disease was often considered as a subtype of Sjögren's syndrome (SS). Clinical and immunologic differences between Mikulicz's disease and SS may warrant further consideration of Mikulicz's disease as a specific autoimmune phenomenon separate from SS, and Mikulicz's disease may be amenable to different treatment modalities than those employed in patients with SS. (Eur J Ophthalmol 2006; 16: 199-203)*

KEY WORDS. *Lacrimal gland swelling, Mikulicz's disease, Salivary gland swelling, Syndrome*

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INTRODUCTION

The first description of Mikulicz's disease was reported in 1892 by Johann von Mikulicz-Radecki, who described a case of a 42-year-old farmer named Christof Calweit with painless and symmetric bilateral lacrimal, parotid, and submandibular gland enlargement associated with lymphocytic infiltrations upon microscopic examination (1). Schaffer in 1927 termed this syndrome of benign and chronic glandular swelling as Mikulicz's syndrome when associated with other entities such as tuberculosis, sarcoidosis, and lymphoma, and as Mikulicz's disease when idiopathic (2).

In 1933, the Danish ophthalmologist Henrik Sjögren introduced the term keratoconjunctivitis sicca in describing the clinical and histologic findings in 19 women with dry mouth and dry eyes, two of whom also displayed swelling of major salivary glands, hence establishing the syndrome

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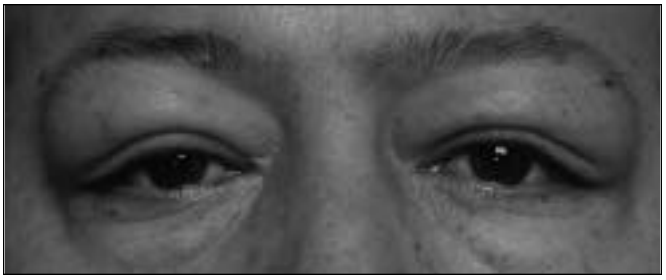

Fig. 1 - *Case 1. A 41-year-old man presented with a chief complaint of eye swelling. The examination was notable for bilateral lacrimal gland swelling that was mobile and non-tender. There is also parotid gland swelling.*

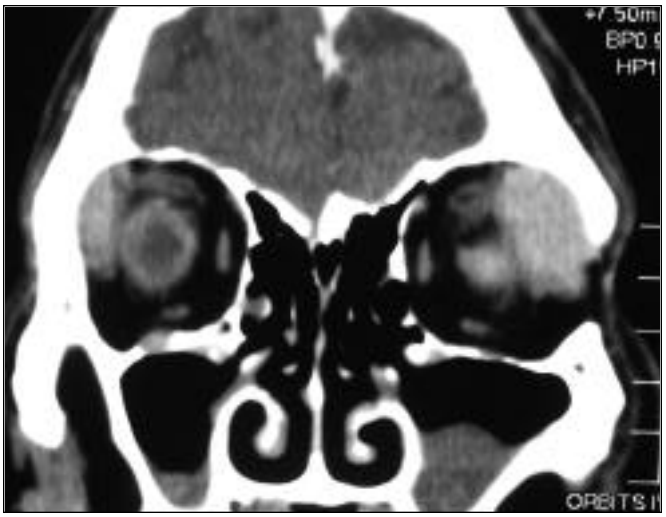

Fig. 2 - *Case 2. A 52-year-old man was evaluated for a 2-year history of bilateral lacrimal, parotid, and submandibular gland enlargement. Coronal image demonstrating enlargement of both lacrimal glands.*

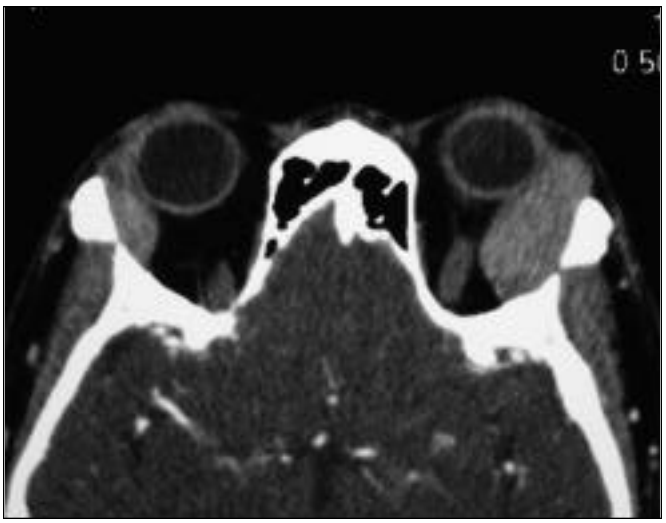

Fig. 3 - *Case 2. Axial image demonstrating diffuse enlargement of both lacrimal glands.*

that bears his name (3). Twenty years later, Morgan and Castleman revived interest in Mikulicz's disease when they concluded that the histologic findings of patients with Mikulicz's disease and with Sjögren's syndrome (SS) were similar, where both were characterized by a pattern of lymphocytic infiltration of the salivary and lacrimal glands. This led to the acceptance of Mikulicz's disease and SS being considered as the same entity. Since that time, many researchers have considered Mikulicz's disease at most a subtype within the larger symptom complex of primary SS. It is only in recent years that the clinical and immunologic differences between Mikulicz's disease and SS have been elucidated (4).

Both Mikulicz's disease and SS show mononuclear infiltration of the lacrimal and salivary glands, but the phenotype and antibody specificities of the conditions are very different. There are also clinical differences. Patients with Mikulicz's disease have normal ocular surfaces and respond well to stimulation by secreting reflex tears, while patients with SS may have squamous metaplasia of the ocular surface and lose the capacity for basic and reflex tearing.

Patients with Mikulicz's disease also have lower frequencies of xerostomia as opposed to patients with SS. Recently, Tsubota et al compared the lacrimal gland function and the pathologic changes of Mikulicz's disease and SS and reported that in Mikulicz's disease, the lacrimal gland acinar cells maintained their function and underwent apoptosis at a lesser frequency when compared to those of SS. Lymphocytes from SS lacrimal glands showed a greater expression of Fas and Fas-L, suggesting that while both entities involve infiltration by lymphocytes, the acinar cells of SS were more likely to undergo apoptosis (5). Yamanato et al undertook a histopathologic analysis of the differences between Mikulicz's disease and SS, and showed that the pathogenesis of Mikulicz's disease involves an IgG4-related systemic process different from that of SS (4).

Such findings may account for the clinical differences between Mikulicz's disease and SS and warrant further consideration of Mikulicz's disease as a specific autoimmune phenomenon that may be amenable to different treatment modalities than those employed in patients with SS.

Herein, we present a series of two cases, with a focus on the clinician's approach to patients with Mikulicz's disease, and suggest a new diagnostic framework for Mikulicz's disease.

METHODS

All cases of Mikulicz's disease presenting to the Jules Stein Eye Institute from January 1999 to December 2004 were located on the electronic medical record system of the orbital clinic. The study was a retrospective nonrandomized consecutive case series. We noted two cases of Mikulicz's disease.

A Medline search using key words "Mikulicz's disease/syndrome/benign lymphoepithelial lesion/lacrimal and salivary gland swelling" was performed from the 1966 to the 2005 database.

The diagnosis of Mikulicz's disease was based on the following criteria: 1) symmetric and persistent swelling of the lacrimal glands and either or both of the parotid or submandibular glands; and 2) the exclusion of other diseases that may mimic this presentation, such as sarcoidosis, viral infection, or lymphoproliferative disorders.

A thorough medical history was taken focusing especially on symptoms of various autoimmune disorders. Patients underwent a full ophthalmological evaluation with a special focus on the evaluation of tear film and ocular surface. Examinations of the skin and oropharyngeal tract were also undertaken.

Written consent for use of the information in these cases was obtained from the patients in accordance with the declaration of Helsinki.

RESULTS

Case 1

A 41-year-old man initially presented with a chief complaint of bilateral eye swelling and ache. Historical evaluation was unremarkable for any systemic illnesses. The examination was notable for bilateral lacrimal gland swelling that was mobile and non-tender (Fig. 1). It was also noted that he had mild bilateral non-tender parotid gland swelling, which he stated had been increasing over a period of 18 months. A previous lacrimal gland biopsy 6 months prior to diagnosis had shown only nonspecific inflammatory infiltrate with occasional mononuclear cells. The ocular examination was otherwise normal. Best-corrected visual acuity was 20/15 in both eyes. There was no history of dry eye and no tear film abnormality. No signs or symptoms of xerostomia were present. A computed tomography scan had been previously performed, which showed diffuse, symmetric enlargement of the lacrimal and parotid glands without lymphadenopathy or other orbital processes. Systemic examination was unremarkable, and hematologic investigations for vasculitides, sarcoidosis, systemic lupus erythematosus, and lymphoproliferative disorders were negative. The patient was not specifically troubled by the orbital ache or swelling, and his symptoms improved with a 1-week course of ibuprofen. The patient had not been given a trial of any medications including steroids. There has not been any progressive increase in the swelling or other persistent inflammation since the diagnosis with a follow-up of 4 years.

Case 2

A 52-year-old man with a history of diabetes mellitus was evaluated for a 2-year history of bilateral lacrimal, parotid, and submandibular gland enlargement. The patient did not complain of pain, and his vision and tearing were not affected. The only significant examination finding was mild proptosis of the left eye by 2 mm. Best-corrected visual acuity was 20/20 bilaterally. No xerostomia was noted. Again, a previously performed computed tomography scan had shown glandular enlargement without other significant features (Figs. 2, 3). On magnetic resonance imaging, there was some enhancement of the parotid glands with gadolinium. Two years prior to presentation, the patient had undergone excision of the right submandibular gland, which showed chronic sclerosing sialadenitis with some reactive hyperplasia. There was no sign of a ductal stone to account for these changes. There were no other clinical features to suggest the need for further evaluation, and the patient has remained stable for 48 months. No treatment was required.

DISCUSSION

In the recent past, Mikulicz's disease has been considered at most a subset of SS, with some researchers classifying it as SS with glandular swelling. However, the diagnosis of SS itself is often quite difficult, for the severity of xerostomia may be difficult to quantify and labial gland biopsy is usually not performed. Moreover, the tissue obtained may be inadequate, and pathologists without much experience in reading such samples may provide incorrect interpretations (6). The development of specific laboratory tests such as antinuclear antibodies (ANA) has

been useful in diagnosis but lacks specificity (7). At times, other conditions may cause symptoms and signs of SS, the so-called secondary Sjögren's disease.

It has been recently noted that the mononuclear infiltrate seen in the lacrimal and salivary glands of patients with Mikulicz's disease and those with SS is different. Patients with Mikulicz's disease are also noted to have very high plasma levels of circulating IgG4, which make up a significant proportion of circulating IgG4. This is not seen in patients with SS. There is also minimal destruction of the glandular architecture in Mikulicz's disease as opposed to in SS (4).

At times, biopsy of the glands may show a gradation of changes ranging from mainly normal architecture, as seen in Mikulicz's disease, to a more lymphoid proliferation, as seen in SS. In between these presentations may lie the condition that some have termed benign lymphoepithelial lesion (8). This is a term that should not be used synonymously with Mikulicz's disease. The lymphoid proliferations of the salivary glands and also the lacrimal glands fall more within the category of MALT lymphoma, although often a reactive lymphoid proliferation is difficult to separate from a neoplastic one in its early stages (9).

There are also important clinical differences between SS and Mikulicz's disease. In Mikulicz's disease, there is minimal keratoconjuctivitis sicca and xerostomia. Neither of our two patients had these symptoms. Patients with Mikulicz's disease are also negative for anti-SS-A or anti-SS-B antibodies that are seen in those with SS. Again, this was the case in our patients. There is a predilection of SS for females, with a female to male ratio of 20:1, which is not seen in Mikulicz's disease. Indeed, both our cases were male.

The areas often targeted in Mikulicz's disease have direct entry into the mucocutaneous areas of the body. There is mucosal tolerance seen in areas where the external environment impacts on the body's immune system. The mucosal structures and the associated exocrine glands are integral to processing environmental antigens in a way that both protects the body from pathogens as well as from itself via the avoidance of autoimmune reactions that can be stimulated by some antigens. These mucosal immune mechanisms are seen in the gut, oropharynx, eye, and skin.

While we may need to consider Mikulicz's disease as an IgG4 mediated autoimmune disorder separate from SS, the triggering antigen remains unknown. IgG4 has been shown to react to lipopolysaccharide, and it may be possible that in these patients, there may be an infective trigger to the condition, perhaps an oral commensal. It is possible that a particular antigen may, combined with a genetic predisposition, lead to a cascade of reactions that set off the autoimmune pathway. If this pathogenesis is proven, it may provide some interesting strategies for treatment.

At this time, IgG4 autoimmunity as a postulated mechanism for Mikulicz's disease has also been linked to retroperitoneal fibrosis, pemphigus vulgaris, sclerosing pancreatitis, and membranous nephropathies. Neither of our patients had other systemic problems.

It may be reasonable to propose diagnostic criteria for Mikulicz's disease that are simply clinically based. Often the history and examination make further examinations unnecessary. A history of chronic, progressive, and painless enlargement of the lacrimal glands, as well as either the parotid or submandibular glands, should suggest the diagnosis. If there are no symptoms or signs of xerostomia or dry eyes, then SS is unlikely. A full history and physical examination can eliminate the possibilities of sarcoid or lymphoproliferative disorder, and in the cases of an atypical presentation, a lacrimal gland biopsy checking specifically for IGg4 stained cells and normal architecture may be useful.

In summary, Mikulicz's disease is a condition in which there is bilateral lacrimal and salivary gland swelling that is not associated with other systemic disorders. The condition is self-limiting and most often, the diagnosis is a clinical one. Useful investigations may include the immunoglobulin titers of IgG4 in peripheral blood. This may be a useful confirmatory test without the need for an invasive biopsy.

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