10.5005/jp-journals-10001-1243

ORIGINAL RESEARCH

Diagnostic and Management Challenges in Mikulicz Syndrome

[1]Abhinandan Bhattacharjee, [2]S Uddin, [3]Rudra Prakash, [4]Aakansha Rathor, [5]Sanchita Kalita

ABSTRACT

Mikulicz disease (MD) is a disorder characterized by multiple lymphoepithelial lesions involving lacrimal and salivary glands. It is an uncommon condition, and very few cases are reported in the literature. It is a variant of Sjögren syndrome (SS) with patients presenting with clinical features over a wide range of spectrum. It is important to differentiate on which side of the disease spectrum the patient is presenting, i.e., either primary SS or secondary SS, because management can vary.

The purpose of mentioning these two cases and its importance lie in the fact that the patients presented at two ends of the spectrum of SS – the first patient belonging to secondary SS and the second patient belonging to primary SS – which changes the line management for both patients, conservative and surgical respectively. The purpose of reporting these two cases is to emphasize the importance of identifying disease symptoms and signs early, which can help stratify the patient as a variant of primary SS or secondary SS and thus decide on the appropriate line of management, saving precious time and discomfort to the patient.

Here we are mentioning two case reports of MD belonging to diagonally opposite spectrums of SS and their management with successful remission.

Keywords: Mikulicz disease, Sjögren syndrome, Superficial parotidectomy.

How to cite this article: Bhattacharjee A, Uddin S, Prakash R, Rathor A, Kalita S. Diagnostic and Management Challenges in Mikulicz Syndrome. Int J Head Neck Surg 2015;6(4): 139-145.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Mikulicz disease (MD) was first described by Dr. Mikulicz in the year 1888, when he reported a 42-year-old East Prussian farmer with swelling of parotid, submandibular, and lacrimal glands. The condition is regarded to be a variant of a larger symptom complex – Sjögren syndrome (SS) because of their similar pathologic characteristics.[1,2] Henrik Samuel Conrad Sjögren, a Stockholm ophthalmologist, described 19 patients with joint deformity and diminished tear production leading to corneal ulceration and was regarded as SS. The essential difference between MD and SS lies in their histological characteristics. Both MD and SS are characterized by dense infiltration of lymphocytes of salivary and lacrimal glands, and abnormal serum antibodies, such as anti-Ro and anti-La,[3,4] but elevated serum IgG4 is seen only in MD.[5]

[1]Assistant Professor, [2]Professor, [3-5]Postgraduate Teacher

[1-5]Department of ENT, Silchar Medical College and Hospital Silchar, Assam, India

Corresponding Author: Abhinandan Bhattacharjee, Assistant Professor, Department of ENT, Silchar Medical College and Hospital, Silchar, Assam, India, Phone: +913842242784 e-mail: dr_abhinandan1@rediffmail.com

CASE REPORTS

Case 1

A 61-year-old female patient presented with a swelling on the right parotid and submandibular regions along with another swelling in the left upper eyelid of 1.5 years' duration. Both the swelling gradually increased in size with mild pain, which was referred to the right ear. This was followed by another swelling involving the left parotid and submandibular regions and a painless swelling in the left groin for 1 year. Local examination revealed multiple, firm, mobile, nontender, well-defined swelling over both parotid and submandibular regions (Fig. 1A), right side of the neck, over both the upper eyelids, and both sides of the groin. The patient had gradually diminishing vision with dryness and irritation of both eyes and associated dryness of the mouth. An oral

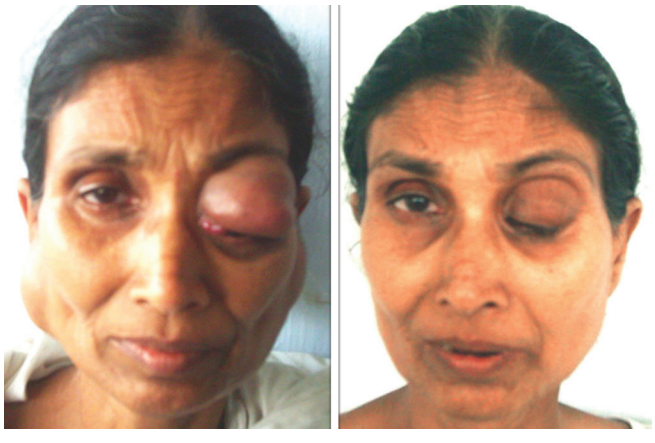

Fig. 1A: Clinical picture of case 1 before and after treatment with I/V steroid

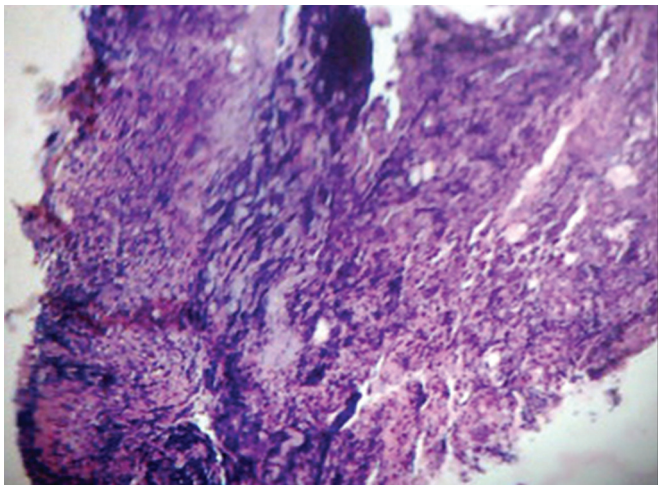

Fig. 1B: Histopathological examination (H&E stain) from left parotid showing lymphoid infiltration and fibrosis

examination revealed no other abnormality except dryness in the oral mucosa. Our patient also had difficultly in talking and hoarseness of voice. Histopathological examination from left parotid and labial biopsy showed lymphoid infiltration and fibrosis consistent with MD (Fig. 1B). A provisional diagnosis of MD was made and the patient was started on intravenous steroids following which there was dramatic resolution and the patient recovered. The disease relapsed after 1 year, which responded similarly well to steroids.

Case 2

A 38-year-old female presented with bilateral infraauricular swelling since 4 years. Both swellings were initially small in size and gradually increased to 7×8 cm in size on the right side and 6×5 cm on the left side extending from the tragus to the angle of mandible. The swellings were soft, freely mobile with hyperpigmented overlying skin and no palpable lymph nodes (Fig. 2A). There was associated dryness of mouth and hoarseness of voice but no dryness of eyes. The patient also had excoriating lesions on bilateral elbows and extensor aspect of lower limbs with no purpura or ecchymosis (Fig. 2B). Dermatological histology showed features of spongiotic dermatitis. An incisional biopsy from the left parotid revealed lymphoepithelial infiltration of stroma and keratinous cyst formation (Fig. 3). A diagnosis of MD with contact dermatitis was made. A course of intravenous steroid followed by oral steroid for 3 weeks was tried, but it did not show complete resolution of the swelling. To improve the cosmetic aspect, bilateral superficial parotidectomy was done as a two-staged procedure with favorable outcome.

DISCUSSION

Pathophysiology

Sjögren syndrome is believed to be a chronic inflammatory disease with autoimmune cause. When the antigen

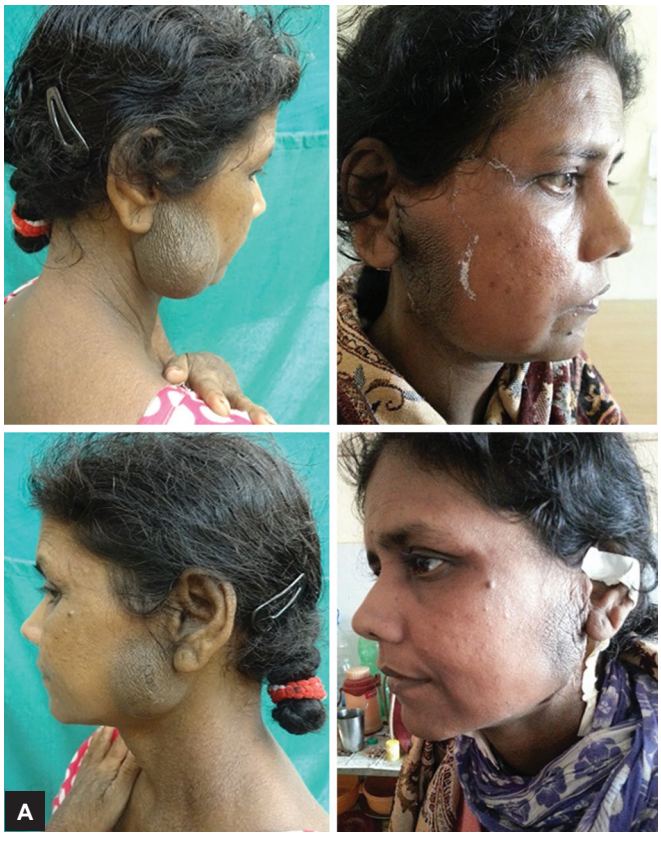

Fig. 2A: Clinical photo of case 2 before and after bilateral superficial parotidectomy

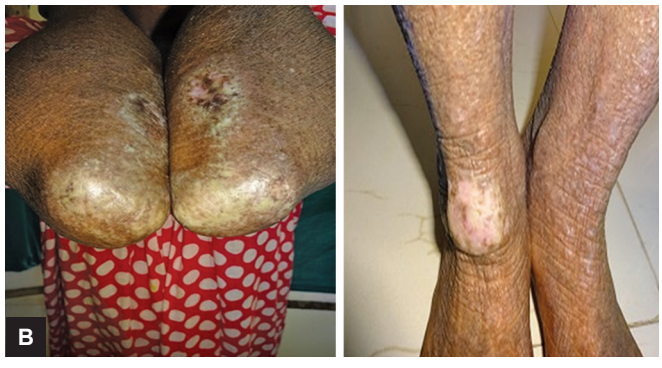

Fig. 2B: Skin lesion of extensor surfaces showing spongiotic dermatitis

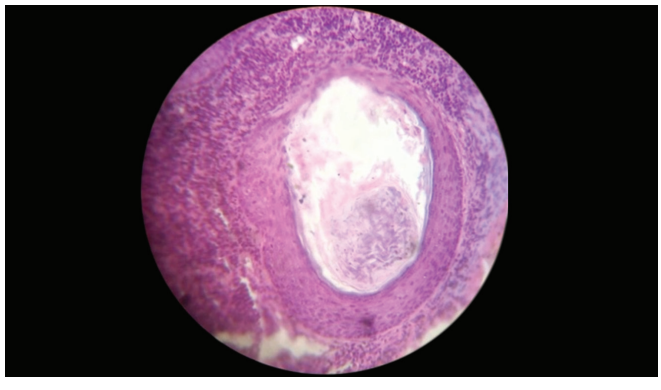

Fig. 3: Histopathological examination from left parotid (case 2) showing dense lymphocytic infiltration and fibrosis

released from the damaged acini (by viruses) comes into contact with lymphatic tissue (normally present within parotid, lacrimal, and minor salivary glands of lips and palate), this results in the production of antibodies that in turn damage more acinar epithelium, continuing the cycle. There is initial periductal small-lymphocyte infiltration. Later large lymphocytes and reticular cells appear. The acinar tissue is totally replaced and epimyoepithelial islands arising from ductal proliferation are scattered throughout the tissue.

Factors in favor of the autoimmune nature of the disease are:

- Association of systemic lupus erythematosus (SLE), scleroderma, rheumatoid arthritis, and rheumatoid factor in over 75% cases
- Presence of dendritic cells, complex organization of inflammatory infiltrate into well-defined B-cell proliferation centers, and activated interfollicular T areas[6]
- Upregulation of HLA-DR on salivary gland epithelial cells from probable viral trigger
- Secretion of proinflammatory cytokines by lymphocytes
- Imbalance between the downregulated apoptosis-inhibitor Bcl-2 and the upregulated apoptosis-inducer Bax, or the autocrine and/or paracrine Fas/FasL interaction[7] resulting in Fas- and caspase-mediated alpha fodrin proteolysis in SS[8]
- Failure to remove autoimmune T cells at the level of thymic selection due to polyclonal B-cell activation
- Prevalence of HLA-B-8, DR-3, HLA DQ A10501 allele, and DRw52.

CLINICAL MANIFESTATIONS

Mikulicz disease is the second most common autoimmune disease after rheumatoid arthritis (RA), more common in the Northern than the Southern Hemisphere. As seen in our study, patients are primarily women, nine times more likely to be affected than men, and the disease usually presents in the 4th and 5th decades of life, with symptoms appearing to increase with age.[9,10] The diversity of symptomatic expression adds to difficulty in the initial diagnosis (Table 1).

Both our cases had extraglandular site involvement, which is seen in one-third of cases.[8] Xerostomia leads to sore mouth, inability to speak, hoarseness, and difficulty in swallowing and chewing as seen in both our patients. Decreased mucin production predisposes to loss of taste, bacterial and yeast infection with increased risk of caries,[11,12] and oral candidiasis in upto 80% of cases with SS.[13] Studies demonstrated that IgA autoantibodies against mAChR may be considered a new marker for differentiating SS dry mouth from non-SS dry mouth.[14] Xerophthalmia (dry eyes) patients complain of a sandy or gritty feeling under the eyelids associated with other symptoms like burning sensation, accumulation of thick strands at the inner canthi, redness, itchy eyes, fatigue, and increased photosensitivity as seen in the first patient. Clinically, there is decreased tear pool in lower conjunctiva, dilatation of conjunctival vessels, pericorneal injection, and irregularity of corneal image. Diminished secretion of tears attributes to the destruction of corneal and bulbar conjunctival epithelium, defined as keratoconjunctivitis sicca. These symptoms typically worsen during the day due to evaporation of aqueous layer.

Table 1: Revised European multicenter study classification criteria for SS

1	Ocular symptoms: A positive response to at least one of the following questions:
	i Have you had daily, persistent, troublesome dry eyes for more than 3 months?
	ii Do you have a recurrent sensation of sand or gravel in the eyes?
	iii Do you use tear substitutes more than three times day?
2	Oral symptoms: A positive response to at least one of the following questions:
	i Have you had a daily feeling of dry mouth for more than 3 months?
	ii Have you had recurrently or persistently swollen salivary glands as an adult?
	iii Do you frequently drink liquids to aid in swallowing dry food?
3	Ocular signs: A positive result for at least one of the following two tests:
	i Schirmer's test: Performed without anesthesia (≤5 mm in 5 minutes)
	ii Rose Bengal ocular dye score (≥4 according to Bijsterveld's scoring)
4	Histopathology: In minor salivary glands (focal lymphocytic sialadenitis), with a focus score ≥1, defined as the number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.
5	Salivary gland involvement: A positive result for at least one of the following diagnostic tests:
	i Unstimulated whole salivary flow (≤1.5 mL in 15 minutes)
	ii Parotid sialography showing the presence of diffuse sialectasis (punctuate activity or destructive pattern), without evidence of obstruction in the major ducts
	iii Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer.
6	Autoantibodies: In serum of antibodies to Ro (SSA) or La (SSB) antigens or both.

In our study, both the cases had clinically significant salivary gland enlargement, which is otherwise seen in 20% of cases. It is nearly always in the parotid gland (bilateral), which is also seen in our cases. There is 40% chance of developing lymphoma. In children, recurrent parotid swelling is a common feature of primary SS.[15] Other ear, nose, and throat (ENT) manifestations are nasal crusting, persistent cough, dyspnea (interstitial lung disease), and sensory neural hearing loss[16] (due to anticardiolipin AB).

Skin-related symptoms in SS usually show palpable purpura with leukocytoclastic vasculitis and associated rheumatoid factor.[17,18] There is overwhelming predominance of small- *vs* medium-vessel vasculitis with a higher prevalence of extraglandular and immunologic SS features.[19] However, dermatological affection seen in our patient (case 2) was that of contact dermatitis showing spongiotic dermatitis in histopathological examination without any form of cutaneous vasculitis. Urticarial vasculitis, anetoderma, and subcutaneous amyloid are also seen in SS.[20-22] Annular erythema is also a feature, which is more common in the Japanese.[23]

Patients with SS also present with musculoskeletal manifestations, such as fatigue, general malaise, Jaccoud's arthropathy, arthralgia, myalgia, and low-grade fever, as seen in our case 1.

OTHER SYMPTOMS

Gastrointestinal symptoms include esophageal mucosal atrophy, atrophic gastritis, subclinical pancreatitis, and primary biliary cirrhosis.[24] Neurologic involvement occurs in approximately 20% of patients with primary SS.[25] Patients may present with hemiparesis, transverse myelopathy, hemisensory deficits, seizures, movement disorders, and aseptic meningitis; multiple sclerosis, carpal tunnel syndrome, and cranial neuropathy may occur.[26] Effects of serum IgG autoantibodies on cerebral mAchRs have some role in the pathogenesis.[27] More than one-third of patients may present with Raynaud's phenomenon, deep vein thrombosis, and vasculitis involving bladder, lung, and kidney. Patients with SS are also at an increased risk of developing non-Hodgkin's lymphoma, primarily of B-cell origin.[28] Genitourinary involvement shows distal renal tubular acidosis, interstitial nephritis, membranous or membranoproliferative, glomerulonephritis immune complex glomerulonephritis.[29] Women with SS may have history of recurrent miscarriages and stillbirths.

DIAGNOSTIC WORK-UP

Hematological investigations commonly reveal mild normochromic, normocytic anemia with raised Erythrocyte sedimentation rate in about 70% cases, as also seen in our case. Rheumatoid factor was found to be positive in case 1. Positive RH factor is typically found in most patients with SS, even when they do not have rheumatoid arthritis (RA).

Renal and liver function test results were normal in both cases. Serum transaminases and alkaline phosphatase should be considered for chronic active hepatitis and primary biliary cirrhosis respectively. One-third of patients with SS have high serum levels of mixed monoclonal cryoglobulins (type II), which correlates with higher risk of lymphoma.[30]

Antibodies to SS antigen A (SS-A/Ro) and SS antigen B (SS-B/La) are found in approximately 95 and 87% of primary SS patients respectively.[31] These autoantibodies are associated with earlier onset, longer duration, and recurrence of parotid gland enlargement, splenomegaly, lymphadenopathy, and vasculitis.[32] Anti-neutrophil cytoplasmic antibodies (ANCA) are relatively uncommon in primary SS,[33] and anticardiolipin antibodies are found in a subset of SS patients.[34]

Computed tomography scan of the parotid region of both the cases showed a homogenous mass in both parotids. Sialography is useful to exclude the presence of obstruction or strictures but is nonspecific. Nevertheless, it is useful in staging and evaluating oral component of SS.[35] Salivary flow rate can be assessed by salivary scintigraphy by measuring uptake and secretion of sodium pertechnetate technetium Tc99m. Determination of beta2 microglobulin and Gamma glutamyl transferase (GGT) in saliva and serum is useful for differentiating SS patients from normal subjects but was not excessively good for differentiating pSS from sSS.[36]

Ocular dryness can be assessed by Schirmer's test considering positive result as less than 5 mm wetting of Whatman filter paper in 5 minutes when placed in lower conjunctiva.

Keratoconjunctivitis sicca is confirmed by Rose Bengal staining test, which showed definitive positive result in case 1. Lacrimal gland acinar cells in SS patients stain strongly with Fas and Fas-L stains and not in cases with MD.

Histopathological Examination

Examination of small salivary glands in the biopsy of lower lip represents a "gold standard" for the diagnosis of SS. Labial biopsy of case 1 revealed pink, extracellular, multilayered, homogeneous, and hyaline material. Illic S showed confirmatory diagnosis from labial biopsy in 32% of cases of SS, nonspecific findings in 36% cases, and nonrepresentative in 30% cases. Therefore, surgical technique had to be adequate in order to obtain the representative number of small salivary glands. The biopsy can also determine the intensity of inflammation and tissue destruction in SS and identify other pathological

conditions.[37] The histological differentiating point between MD and SS is the association of prominent infiltration of IgG4 positive plasmocytes in lacrimal and salivary glands[5] as seen in both our cases differentiating it from SS.

In SS of pediatric population, parotid gland biopsy is an effective and safe means of obtaining salivary gland tissue for histologic evaluation.[38] Ultrastructurally, the epimyoepithelial cell islands were sharply demarcated from the surrounding parenchyma by a thick basement membrane containing collagen fibers. The epithelial cells within the islands are united by well-formed desmosomes having prominent tonofilament bundles but no myogenic differentiation.[39] On the contrary, "marginal zone B-cell lymphoma of MALT-type" of the salivary glands produces a dense lymphoid infiltrate with obliteration of acini and the centrocyte-like cells forming broad halos around epithelial nests. Further, lymphoma cells express monotypic surface Ig monoclonal plasma cells.[40]

Diagnosis of MD

Diagnosis of MD can be done upon the following criteria: (1) Visual confirmation of symmetrical and persistent swelling in more than two lacrimal and major salivary glands; (2) prominent mononuclear infiltration of lacrimal and major salivary glands; and (3) exclusion of sarcoidosis and other lymphoproliferative disease.[41] According to the criteria of Schaffer and Jacobsen,[3] MD is of unknown etiology and follows a benign course, whereas SS is associated with some other disorders, such as leukemia, lymphosarcoma, tuberculosis, and sarcoidosis.

Although different classification and diagnostic systems like Revised European Multicenter Study and San Diego criteria are available, we used the San Francisco criteria, which consider an average "focus" (a cluster of 50 or more lymphocytes) score of 2 or more per 4 mm^2 (Table 2).

TREATMENT

Treatment is aimed at providing symptomatic relief and cosmesis. For case 1, being diagnosed as a part of secondary SS, conservative treatment with intravenous prednisolone at a dose of 20 mg twice daily was administered for 1 week, which was tapered gradually and followed up with oral prednisolone. This resulted in gradual regression of parotid and lacrimal swelling offering complete functional and cosmetic improvement (Fig. 1). For case 2, being a part of primary SS, a surgical management of bilateral superficial parotidectomy was done following unsatisfactory response to steroid treatment to start with. Favorable cosmetic outcome was obtained with no recurrence in the long-term.

Other conservative measures like artificial tears for dry eyes with avoidance of dusty, windy, and dry climate; regular sips of water; and artificial saliva for dry mouth were helpful. Temporary plugging of lacrimal puncta with punctal plugs may also help. Newer options are pilocarpine (5 mg PO tid) or cevimeline tablets 30 mg PO tid. Dental hygiene and use of topical fluorides may help retard decay and periodontal disease.

For arthralgia and arthritis, acetaminophen or NSAIDs were given to relieve symptoms. In resistant cases, low-dose methotrexate may be useful to control arthralgia and myalgia.[42] Long-term anticoagulation may be needed in antiphospholipid antibody syndrome and systemic corticosteroids for diffuse interstitial lung disease, glomerulonephritis, vasculitis, and interstitial nephritis.[43] In cases of acute or chronic myelopathy, axonal sensorimotor neuropathy or cranial nerve involvement treatment by cyclophosphamide allows partial recovery or stabilization.[41] In cases of malignant MD, especially with regional metastasis, postoperative radiotherapy gives better result.[44]

Follow-up is done every 3 months initially and patients were stable upto 6 months. No complications like

Table 2: San Francisco criteria for primary and secondary SS

Primary SS
1 Focal lymphocytic sialadenitis in minor salivary gland biopsy with focus score >1 focus score/4 mm^2 or benign lymphoepithelial lesion in major SG, and
2 KCS
a Characteristic corneal and conjunctival epithelial staining with Rose Bengal, seen through a slit lamp, and
b Reduced tear meniscus and breakup time, or
c Schirmer's test (without anesthesia) ≤5 mm/5 minutes
Secondary SS
1 Rheumatoid arthritis or other connective tissue disease diagnosed by established criteria, and
2 One or both of the criteria for primary SS described above
Possible SS
1 One component of primary SS described above
2 Presence of any of the following: Pulmonary lymphocytic interstitial infiltrates, interstitial nephritis and/or renal tubular acidosis, purpura (with hypergammaglobulinemia or vasculitis), chronic liver disease (not cirrhosis or infectious), peripheral neuropathy, hypergammaglobulinemia (poly or monoclonal) with anti-Ro/SS-A and/or anti-La/SS-B

SLE, RA, parotitis, emergence of parotid tumors, neonatal lupus and congenital heart block, or antiphospholipid syndrome were observed.

CONCLUSION

Mikulicz disease can present as a distinct entity or in between the spectrum of primary SS or secondary SS. As seen in our case 1, a patient who presented with xeropthalmia and xerostomia responded to steroids, making it behave as secondary SS. However, our case 2, which was primary SS, presented with xerostomia but no xeropthalmia and did not respond to steroids. Hence, surgical treatment was carried out with satisfactory outcome. Thus, differentiating between MD and SS of primary and secondary variants is important to determine the line of treatment and save precious time and risk of untoward distress to the patient. Sjögren syndrome is a common autoimmune disease evidenced by broad organ-specific and systemic manifestations, the most prevalent being diminished lacrimal salivary gland function, xerostomia, KCS, and parotid gland enlargement. Primary SS presents alone and secondary SS occurs in connection with autoimmune rheumatic diseases. In addition, symptoms do not always present concurrently. This diversity of symptomatic expression adds to the difficulty in initial diagnosis. Armed with the recently framed criteria for diagnosis, specialists, such as rheumatologists, primary care physicians, ophthalmologists, and otolaryngologists who would otherwise focus only on those symptoms that encompass their areas of expertise can get a comprehensive image of the presenting patient, leading to early identification and treatment of SS. Where immunohistological and other modern diagnostic tools are not available, histopathological examination of labial mucosa and the salivary gland itself along with its clinical features can provide reasonable confirmation of the diagnosis and aid in the management of this autoimmune disease.

REFERENCES

1. Morgan W, Castleman B. A clinicopathologic study of Mikulicz's disease. Am J Pathol 1953 May-Jun;29(3):471-503.
2. Morgan W. The probable systemic nature of Mikulicz's disease and its relation to Sjögren syndrome. N Engl J Med 1954 Jul;251(1):5-10.
3. Schaffer A, Jacobsen A. Mickulicz's syndrome – a report of ten cases. Am J Dis Child 1927 Sep;34(3):327-346.
4. Talal M, Bunim J. The development of malignant lymphoma in the course of Sjögren's syndrome. Am J Med 1964;36:529-540.
5. Yanamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yanamoto H, Takahashi H, Imai K. Clinical and pathological differences between Mickulicz's disease and Sjogren's syndrome. Rheumatology 2005 Feb;44(2):227-234.
6. Andrade RE, Hagen KA, Manivel JC. Distribution and immunophenotype of the inflammatory cell population in benign lymphoepithelial lesion (MD). Hum Pathol 1988 Aug;19(8):932-941.
7. Manganelli P, Fietta P. Apoptosis and Sjögren syndrome seminars in arthritis and rheumatism. Semin Arthritis Rheum 2003 Aug;33(1):49-65.
8. Hayashi Y, Arakari R, Ishimura N. Apoptosis and estrogen deficiency in primary Sjögren syndrome. Curr Opin Rheumatol 2004 Nov;16(5):552-556.
9. Bloch BW, Wohl MJ, Bunim JJ. Sjögren's syndrome: a clinical pathological and serological study of sixty-two cases. Medicine (Baltimore) 1965 May;44(3):187-231.
10. Pillemar SR, Matteson EL, Jacobsson LT, Martens PB, Melton LJ 3rd, O'Fallon WM, Fox PC. Incidence of physician-diagnosed primary Sjögren syndrome in residents of Olmsted County, Minnesta. Mayo Clin Proc 2001 Jun;76(6):593-599.
11. Van der Reijden WA, Vissink A, Veerman ECI, Amerongen AVN. Treatment of oral dryness related complaints in Sjögren's syndrome. Ann Rheum Dis 1999;58(8):465-473.
12. Slomiany BL, Murty VL, Piotrowski J, Slomiany A. Salivary mucins in oral mucosal defence. Gen Pharmacol 1996 Jul; 27(5):761-771.
13. Rehman HU. Sjögren's syndrome. Yonsei Med J 2003 Dec 30;44(6):947-954.
14. Berra A, Sterin-Borda L, Bacman S. Role of salivary IgA in the pathogenesis of Sjögren syndrome. Clin Immunol 2002 Jul;104(1):49-57.
15. Cimaz R, Casadei A, Rose C, Bartunkova J, Sediva A, Falcini F, Picco P, Taglietti M, Zulian F, Ten Cate R, et al. Primary Sjögren syndrome in paediatric age: a multicentre survey. Eur J Pediatr 2003 Oct;162(10):661-665.
16. Tumiati B, Casoli P, Parmeggiani A. Hearing loss in the Sjögren syndrome. Ann Intern Med 1997 Mar;126(6):450-453.
17. Fox RI, Carson DA, Chen P, Fong S. Characterisation of a cross reactive idiotype in Sjögren's syndrome. Scand J Rheum 1986;561 (Suppl):83-88.
18. Alexander EL, Provost TT. Cutaneous manifestation of primary Sjögren's syndrome. A reflection of vasculitis and association with anti-Ro (SSA) antibodies. J Invest Dermatol 1983 May;80(5):386-391.
19. Ramos-Casals M, Anaya JM, García-Carrasco M, Rosas J, Bové A, Claver G, Diaz LA, Herrero C, Font J. Cutaneous vasculitis in primary Sjögren syndrome: classification and clinical significance of 52 patients. Medicine (Baltimore) 2004 Mar;83(2):96-106.
20. Pablos JL, Cogolludo V, Pinedo F, Carriera PE. Subcutaneous nodular amyloidosis in Sjögren's syndrome. Scand J Rheumatol 1993;22(5):250-251.
21. Ricci RM, Meffert JJ, McCollough ML. Primary anetoderm. Cutis 1998 Aug;62(2):101-103.
22. O'Donnell B, Black AK. Urticarial vasculitis. Int Angiol 1995 Jun;14(2):166-174.
23. Ruzicka T, Faes J, Bergner T, Peter RU, Braun-Falco O. Annular erythema associated with Sjögren's syndrome: a variant of systemic lupus erythematosus. J Am Acad Dermatol 1991 Sep;25(3):557-560.
24. Skoupuli FN, Barbatis C, Moustopoulos HM. Liver involvement in primary Sjögren's syndrome. Br J Rheumatol 1994 Aug;33(8):745-748.
25. Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, Dubucquoi S, Pruvo JP, Vermersch P, Hatron PY. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 2004 Sep;83(5):280-291.

26. Malinow KL, Molina R, Gordon B, Selnes OA, Provost TT, Alexander EL. Neuropsychiatric dysfunction in primary Sjögren's syndrome. Ann Intern Med 1985 Sep;103(3):344-350.
27. Reina S, Sterin-Borda L, Orman B, Borda E. Autoantibodies against cerebral muscarinic cholinoceptors in Sjögren syndrome: functional and pathological implications. J Neuroimmunol 2004 May;150(1-2):107-115.
28. Kassan SS, Thomas T, Moutsopoulos HM. Increased risk of lymphoma in primary in sicca syndrome. Ann Intern Med 1978;89(6):888-892.
29. Kassan SS, Talal N. Renal disease with Sjögren's syndrome. In: Talal N, Moutsopoulos HM, Kassan SS, editors. Sjogren's syndrome: clinical and immunological aspects. Berlin: Springer Verlag; 1987. p. 96.
30. Tzioufus AG, Boumba DS, Skopouli FN, Moutsopoulos HM. Mixed cryoglobulinemia and monoclonal rheumatic factor cross-reactive idiotypes as predicting factors for development of lymphoma in primary Sjogren's syndrome. Arthritis Rheum 1996 May;39(5):767-772.
31. Manoussakis MN, Moutsopoulos HM. Sjogren's syndrome. Otolaryngol Clin North Am 1999 Oct;32(5):843-860.
32. Manoussakis MN, Tzioufus AG, Moutsopoulos HM. Serological profiles in subgroups of patients with Sjogren's syndrome. Scand J Rheumatol 1986;61 (Suppl):89-92.
33. Merkel PA, Polisson RP, Chang Y, Skates SJ, Niles JL. Prevalence of ANCA in a large inception cohort of patients with connective tissue disorder. Ann Intern Med 1997 Jun 1; 126(11):866-873.
34. Asherso RA, Fei HM, Staub HL, Khamashta MA, Hughes GR, Fox RI. Antiphospholipid antibodies and HLA association in primary Sjogren's syndrome. Ann Rheum Dis 1992 Apr;51(4):495-498.
35. Kalk WW, Vissink A, Vissink A, Spijkervet FK, Bootsma H, Kallenberg CG, Roodenburg JL. Parotid sialography for diagnosing Sjögren syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002 Jul;94(1):131-137.
36. Castro J, Jimenez JA, Sabio JM, Sánchez-Román J. Salivary and serum β_2-microglobulin and γ-glutamyl-transferase in patients with primary Sjögren syndrome patients and Sjögren syndrome secondary to systemic lupus erythematosus. Clinica Chimica Acta 2003 Sept;334(1-2):225-231.
37. Illic S, Arsic L, Milosavljevic, Strbac M, Tomasevic G. Diagnosis of Mikulicz-Sjögren syndrome using biopsy of the minor salivary glands. Vojnosanitetski Preglad 2002 Nov-Dec;59(6):615-620.
38. McGuirt WF, Whang C, Moreland W. Role of parotid biopsy in the diagnosis of paediatric Sjögren syndrome. Arch Otolaryngol Head Neck Surg 2002 Nov;128(11):1279-1281.
39. Kahn LB. Benign lymphoepithelial lesion (Mikulicz's disease) of the salivary gland: an ultrastructural study. Hum Pathol 1979 Jan;10(1):99-104.
40. Carbone A, Gloghini A, Ferlito A. Pathological features of lymphoid proliferations of the salivary glands: lymphoepithelial sialadenitis versus low-grade B-cell lymphoma of the malt type. Ann Otol Rhinol Laryngol 2000 Dec;109(12 Pt 1):1170-1175.
41. Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, Dubucquoi S, Pruvo JP, Vermersch P, Hatron PY. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 2004 Sep;83(5): 280-291.
42. Skopouli FN, Jagiello P, Tsifetaki N, Moutsopoulos HM. Methotrexate in primary Sjögren's syndrome. Clin Exp Rheumatol 1996 Sep-Oct;14(5):555-558.
43. Shimoyama K, Ogawa N, Sawaki T, Karasawa H, Masaki Y, Kawabata H, Fukushima T, Wano Y, Hirose Y, Umehara H. A case of Mikulicz's disease complicated with interstitial nephritis successfully treated by high-dose corticosteroid. Mod Rheumatol 2006;16(3):176-182.
44. Cheng GY. Malignant change in lymphoepithelial lesion of the parotid gland – report of 3 cases. Chi J Oncol 1986 Jan;8(1):76-77.