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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Jamir Pitton Rissardo, MD, Academic Research, Adjunct Associate Professor, Research Associate, Department of Medicine, Federal University of Santa Maria, Santa Maria 97105110, Brazil. jamirrissardo@gmail.com

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CASE REPORT

Cutaneous mucosa-associated lymphoid tissue lymphoma complicating Sjögren's syndrome: A case report and review of literature

Ying Liu, Jian Zhu, Yan-Hong Huang, Qian-Ru Zhang, Li-Ling Zhao, Ruo-Han Yu

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Ying Liu, Yan-Hong Huang, Qian-Ru Zhang, Li-Ling Zhao, Ruo-Han Yu, Department of Rheumatology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 102218, China

Jian Zhu, Department of Rheumatology and Immunology, The First Medical Center, Chinese PLA General Hospital, Beijing 100853, China

Corresponding author: Jian Zhu, MD, Professor, Department of Rheumatology and Immunology, The First Medical Center, Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. jian_jzhu@126.com

Abstract

BACKGROUND

The association of Sjögren's syndrome (SS) and lymphoma is similar. Mucosa-associated lymphoid tissue (MALT) or extranodal marginal zone B-cell lymphoma was the most common lymphomatous histology in SS patients. MALT in SS patients is frequently located in the parotid gland, while MALT lymphoma of the skin with SS is an exceedingly rare entity that needs to be recognized.

CASE SUMMARY

A 60-year-old woman presented with a 3-year history of progressive dry mouth associated with a 1-year history of enlarging cutaneous nodules. Physical examination revealed two hard subcutaneous nodules on her right lower leg. The results of Schirmer's test were positive, despite the absence of dry eyes. Labial salivary gland biopsy revealed lymphocytic infiltration and chronic inflammation with a focus score of 2. The patient was diagnosed with SS. She underwent resection of one cutaneous nodule, and histopathological analysis identified the nodule as MALT lymphoma. Her dry mouth symptoms improved, and the nodules decreased after 6 mo of treatment with hydroxychloroquine sulfate and chemotherapy (thalidomide, cyclophosphamide, and dexamethasone).

CONCLUSION

Lymphoma is a severe complication of SS, shown by the reported unique case of cutaneous MALT lymphoma with SS.

Key Words: Sjögren's syndrome; Mucosa-associated lymphoid tissue; Lymphoma; Skin;

Nodule; Case report

Core Tip: Lymphoma is a severe complication of Sjögren's syndrome (SS) and mucosa-associated lymphoid tissue (MALT) lymphoma is the most common type. We report a rare case of cutaneous MALT lymphoma with SS. A literature review was performed to provide information on the condition's clinical manifestations and associated extensive sites. Our case highlights that the skin is rarely involved aside from the parotid gland, orbital adnexa, lung, thyroid, and stomach. Patients may have no symptoms; thus, regular physical assessments are required.

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INTRODUCTION

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, compromising lacrimal and salivary gland secretions. Lymphoma is a severe complication of SS. Mucosa-associated lymphoid tissue (MALT) lymphoma, also known as extranodal marginal zone B-cell lymphoma (EMZL), is the most common histologic type in SS patients[1]. The parotid gland is the most frequent location; however, it has also been detected in the lung, thyroid, and stomach[2-4]. To our knowledge, MALT lymphomas involving the skin have not been reported in patients with SS.

CASE PRESENTATION

Chief complaints

A 60-year-old woman was admitted to our rheumatology department due to progressive dry mouth and enlarging cutaneous nodules.

History of present illness

Over the past 3 years, the patient has experienced mild-to-moderate dry mouth without dry eyes or any special medicine. A painless cutaneous nodule was found in her right lower leg 1 year previously, and the nodule had gradually enlarged within the past 6 mo. The nodule was resected, and pathological examination showed a possible lymphoproliferative disease. In the following months, her symptoms of dry mouth were aggravated, and nodules in the right lower leg relapsed with an increase in number. The patient was then referred to our hospital for further examination. She did not have arthralgia, parotid gland swelling, fatigue, decreased appetite, or unintentional weight loss.

History of past illness

The patient's past medical history was unremarkable.

Personal and family history

The patient's personal and family history was also unremarkable.

Physical examination

Physical examination only showed two hard subcutaneous nodules on her right lower leg (Figure 1A).

Laboratory examinations

On admission, laboratory tests showed normal blood cell count, and routine urine, creatinine, coagulation markers, cardiac enzymes, complement, and inflammatory biomarker levels. Elevated alkaline phosphatase (203 U/L, reference range, 35–135 U/L) and gamma-glutamyl transpeptidase (423 U/L, reference range, 7–45 U/L) were noted. Serum tumor markers (CA125, CA153, CA19-9, AFP, CEA, and CYFRA21-1) and viral serology (HIV, HBV, and HCV) was negative. Protein and immunofixation

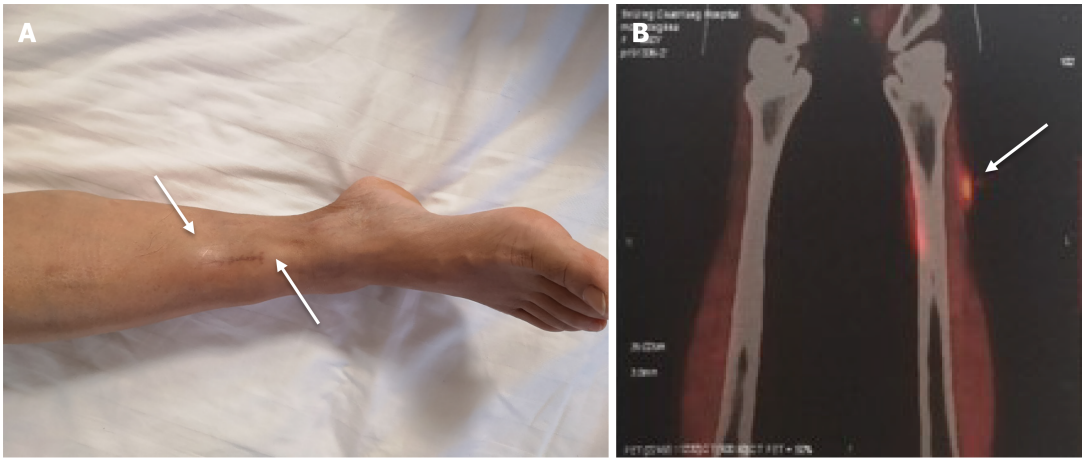

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Figure 1 Appearance of nodules. A: Clinical photograph showing two subcutaneous nodules on the right lower leg (white arrow); B: Positron emission tomography computed tomography scan showing increased fluorodeoxyglucose uptake in an anterolateral tibialis anterior nodule (white arrow).

electrophoreses revealed no evidence of serum monoclonal gammopathy or Bence-Jones proteinuria. Serum-free light-chain levels were normal. Anti-nuclear antibody was positive (1 : 640 centromere pattern), while no Sjögren's syndrome type A antigen (SSA)/Ro or type B (SSB)/La antibodies were detected. The bone marrow aspirate and biopsy results were normal.

Imaging examinations

High-resolution chest computed tomography (CT) did not show any signs of interstitial pneumonitis or mediastinal lymphadenopathy. Positron emission tomography CT demonstrated increased fluorodeoxyglucose uptake in the right anterolateral tibialis anterior, and several nodular shadows (Figure 1B). There were no signs of invasion or spread to the surrounding structures or organs.

Further diagnostic work-up

The Schirmer's test showed positive results, despite the absence of dry eyes. Labial salivary gland biopsy revealed lymphocytic infiltration and chronic inflammation with a focus score (FS) of 2 (Figure 2A). Repeat cutaneous biopsy showed a possible neoplastic infiltration composed of small lymphocytes occupying the marginal zone and plasma cells associated with hyperplastic B-cell follicles at the periphery of the follicle zone (Figure 2B). She was Bcl2- (Figure 3A), CD5-, CD20- (Figure 3B), and PAX5-positive (Figure 3C), and CD3-, CD10-, and Bcl6-negative. Plasma cells were highlighted by CD138 (Figure 3D) and showed clear kappa-light chain restriction (Figure 3E). Immunoglobulin gene rearrangements were positive for IgK (Vk-Jk, Vk-Kde+INTR-Kde) and probably positive for IgH (FR1-JH, FR2-JH).

FINAL DIAGNOSIS

The patient presented with symptoms of oral dryness for more than 3 mo, without a history of head and neck radiation treatment, active hepatitis C infection, AIDS, sarcoidosis, amyloidosis, graft-versus-host disease and IgG4-related disease, and was diagnosed with SS according to the 2016 American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) classification criteria for SS[5]. Primary biliary cholangitis was suspected based on elevated alkaline phosphatase, gamma-glutamyl transpeptidase, and positive anticentromere antibody. Based on the histopathological findings, a MALT cutaneous EMZL was diagnosed. The final diagnosis was cutaneous MALT lymphoma complicating SS.

TREATMENT

The patient was started on 400 mg of hydroxychloroquine sulfate tablets and 500 mg of ursodeoxycholic acid daily. She was then referred to a hematologist for chemotherapy with 100 mg of thalidomide daily, 50 mg of cyclophosphamide on days 1–14, and 20 mg of dexamethasone on days 1–4, 9–12, 17–20, and 25–28 in a 28-d cycle.

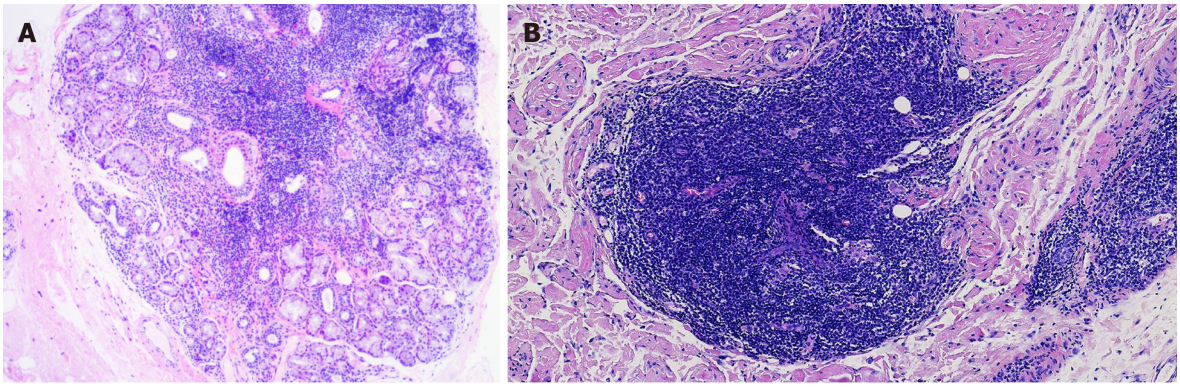

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Figure 2 Hematoxylin and eosin staining. A: Histopathological assessment of salivary gland revealed lymphocytic infiltration and chronic inflammation; B: Infiltration of small-sized lymphocytes occupied the marginal zone.

OUTCOME AND FOLLOW-UP

At the last follow-up (after 6 mo), her symptoms of dry mouth had improved and liver function had normalized. The nodules decreased, and there was no evidence of recurrent lymphoma.

DISCUSSION

We searched for articles from April 2010 to April 2020 for "Sjögren's syndrome (MeSH Terms)" AND "MALT lymphoma (MeSH Terms)" in PubMed. The language was restricted to English. Review articles, articles not reporting on SS with MALT lymphoma, articles about secondary SS, articles missing important information, and articles not found in full text were excluded. In total, 87 articles were identified by the search criteria. Fourteen non-English articles, 11 review articles, 29 not reporting on SS with MALT lymphoma, 3 about secondary SS, and 4 without full texts were excluded from the review. Twenty-six articles (including one prospective study, four retrospective studies, several case reports, and case series) with comprehensive clinical and laboratory data from 142 patients were included and analyzed in detail, including race, age, sex, symptoms, and location of MALT lymphoma[2-4,6-28]. All patients were clinically diagnosed with SS and fulfilled the ACR-EULAR classification criteria[5] or the American-European Consensus Group criteria[29]. The median age at SS diagnosis was 45 years (range, 29–73 years). The mean lymphoma onset age was 54 years (range, 35–74 years). All patients were diagnosed with MALT lymphoma after or simultaneously with SS. Among the 142 patients, 133 were female, 45 (34 missing data) presented with symptoms of dry eyes and xerostomia, 26 (46 missing data) complained of constitutional symptoms (fatigue, decreased appetite, or weight loss), 51 (40 missing data) had parotid gland swelling, while cryoglobulinemia or cryoglobulinemic vasculitis occurred in 10 (65 missing data), 37 had monoclonal gammopathy, 100 (29 missing data) showed Anti-Ro/SSA antibodies, 41 (35 missing data) had anti-La/SSB antibodies, 87 (40 missing data) were rheumatoid factor (RF)-positive, and 31 (65 missing data) had low C4 Levels. Lymphocytic infiltration focus (FS ≥ 1), which is typical for SS, was reported in 36 (87.8%) patients. In addition, 101 (71.1%) patients did not undergo baseline salivary gland biopsy, and 5 (12.2%) patients had negative FS. MALT lymphoma was found in the parotid gland (77.5%), lung (14.8%), thymus (5.6%), lymph nodes (4.2%), bone marrow (3.5%), submandibular glands (2.1%), lacrimal gland (1.4%), and other organs, such as the stomach, breast, tongue, spleen, liver, kidney, and mouth. The detailed patient characteristics are shown in Table 1. The clinical and laboratory data of the 26 cases or case series are summarized in Table 2.

The recently reported frequency of lymphoma complicated with SS in the Asian and East Central European populations are 2.7%–9.8%[30] and 2%[31], respectively. It is estimated that the risk of lymphoma in patients with SS is about nine times higher than that in the general population[32]. MALT is the most common lymphomatous histology in SS patients[1], but nodal marginal zone lymphoma and diffuse large B-cell lymphoma have also been identified[30,32,33]. As MALT lymphoma in patients with SS is rare, its incidence is unclear. The most common sites of MALT lymphomas are the stomach, eye/adnexa, and spleen[34-36]. However, in SS patients, the parotid gland is the most frequent location of MALT lymphoma, as demonstrated by our literature review. It is reported that SS patients have a 1000-fold increased risk of MALT lymphoma of the parotid gland[37]. Other sites of MALT lymphoma in SS, such as the lung[4,7], thymus[12,13], submandibular glands[4,27], breast[6], liver[4], and stomach [4] can also be involved. However, cutaneous MALT lymphomas are exceedingly rare in SS. We confirmed our case as cutaneous MALT lymphoma according to the histopathology and immunoglobulin gene rearrangement findings in the setting of SS. To our knowledge, this is the first reported

Table 1 Clinical characteristics of the 142 Sjögren's syndrome patients with mucosa-associated lymphoid tissue lymphoma reported in the literature

Patients characteristics	SS with MALT lymphoma (*n* = 142)
Age of SS diagnosis, mean year	45
Age of lymphoma onset, mean year	54
Female, *n* (%)	133/142 (93.7)
Dry eye, *n* (%)	45/108 (41.7)
Dry mouth, *n* (%)	45/108 (41.7)
Parotid gland swelling, *n* (%)	51/102 (50.0)
Fatigue, decreased appetite, or weight loss, *n* (%)	26/96 (27.1)
Cryoglobulinemia or cryoglobulinemic vasculitis, *n* (%)	10/77 (13.0)
ANA positive, *n* (%)	104/113 (92.0)
Anti-Ro/SSA positive, *n* (%)	100/113 (88.5)
Anti-La/SSB positive, *n* (%)	41/107 (38.3)
Monoclonal gammopathy, *n* (%)	37/82 (45.1)
RF positive, *n* (%)	87/102 (85.3)
Low C4, *n* (%)	31/77 (40.3)
Positive SG biopsy, FS ≥ 1, *n* (%)	36/41 (87.8)
Lymphoma location Parotid gland, *n* (%)	110 (77.5)
Lung, *n* (%)	21 (14.8)
Thymus, *n* (%)	8 (5.6)
Lymph nodes, *n* (%)	6 (4.2)
Bone marrow, *n* (%)	5 (3.5)
Submandibular glands, *n* (%)	3 (2.1)
Lacrimal gland, *n* (%)	2 (1.4)
Other sites, *n* (%) (stomach, breast, tongue, spleen, liver, kidney, mouth, lip)	9 (6.3)

SS: Sjögren's syndrome; MALT: Mucosa-associated lymphoid tissue; RF: Rheumatoid factor; SG: Salivary gland.

case of cutaneous MALT associated with SS.

SS is characterized by polyclonal lymphocytic infiltration and chronic inflammation of the exocrine glands. In most patients, lymphoproliferation remains confined to the glandular tissue and does not undergo malignant transformation, indicating that the pathological transition to MALT lymphoma is characterized by the expansion of the centrocyte-like B-cell population and the infiltration of B cells aberrantly expressing CD5 and CD43. The precise pathogenic mechanisms of the transition from SS to lymphoma are currently being studied[38]. Differentiating benign lymphoid proliferation and malignant MALT lymphoma can be difficult and requires the integration of morphological, immunohistochemical, and flow cytometric analyses of appropriate biopsy material[39-41]. MALT lymphoma at many sites (including salivary glands) is associated with the presence of lymphoepithelial islands, which become infiltrated by aggregates of neoplastic lymphoid cells. In addition, a diffuse dense infiltrate of CD20 positive cells and destruction of the normal parenchyma of the glands are features supporting lymphoma. As for immunophenotype, the neoplastic cells were positive for CD19 and CD20 and negative for CD10, Bcl-6, and cyclin D1[42]. Immunoglobulin light-chain restriction may also be demonstrated, especially in plasma cells. Molecular diagnostic analysis consisting of PCR-based analysis of immunoglobulin gene rearrangements can also be very helpful in distinguishing EMZL from reactive proliferation. As described in our patient, MALT lymphoma was diagnosed by morphology, immunophenotype, and immunoglobulin gene rearrangements of cutaneous biopsy.

Several studies have recently focused on biomarkers for developing lymphoma during the course of SS. Characteristics, such as persistent salivary gland swelling, low C4, leukopenia, cryoglobulinemia and/or cryoglobulinemic vasculitis, monoclonal gammopathy, and positive RF are considered risk factors[43-45]. De Vita *et al*[4] reported that salivary gland swelling and/or cryoglobulinemia at baseline were more commonly seen in SS patients evolving into lymphoma than in SS controls, and the risk of

Table 2 Literature reviews of 26 published cases or case series

Ref.	*n*	Age of SS diagnosis	Age of lymphoma onset	Sex	Sicca symptom	Risk factor	Anti-SSA/SSB	Lymphoma location	Stage (Ann Arbor)	Treatment	Prognosis
Xu *et al*[3]	4	NA	42	M	–	PGS	SSA/SSB	Parotid gland, thymus	IVA	Surgery	Improved
		NA	49	F	–	PGS, Monoclonal gammopathy, RF	SSA/SSB	Parotid gland, thymus	IVA	Surgery	Improved
		NA	49	F	–	Monoclonal gammopathy	SSA/SSB	Thymus	IVA	Surgery	Improved
		NA	38	F	–	RF	SSA/SSB	Thymus	IA	Surgery	Improved
Belfeki *et al*[6]	1	60	65	F	Dry eye, dry mouth	PGS, Monoclonal gammopathy, low C3, low C4	SSA	Breast	NA	NA	NA
Xian *et al* [7]	1	NA	45	F	NA	NA	NA	Lung	NA	Chemotherapy	Deceased
Arai *et al* [12]	1	NA	66	F	NA	RF	SSA	Thymus	NA	Surgery	Improved
Momoi *et al*[13]	1	52	58	F	NA	RF	SSA	Thymus	NA	Surgery, chemotherapy	Improved
Yoshida *et al*[14]	1	32	NA	F	NA	Monoclonal gammopathy	SSA	Thymus	NA	Surgery, chemotherapy	Improved
Hsu *et al* [15]	1	NA	54	F	Dry eye, dry mouth	NA	SSA	Mouth	IE	Surgery	Improved
De Vita *et al*[16]	1	41	46	F	Dry eye, dry mouth	PGS, cryoglobulins,RF, low C4	SSA/SSB	Parotid gland	IE	Belimumab, RTX	Improved
Kobayashi *et al*[17]	1	31	39	F	Dry eye	NA	SSA/SSB	Lung	I	GS	NA
Taylor *et al* [18]	1	NA	67	F	NA	NA	NA	Lung	NA	Surgery	NA
Baqir *et al* [19]	3	NA	74	F	Dry eye, dry mouth	NA	SSA/SSB	Lung	NA	NA	NA
		NA	48	F	Dry eye, dry mouth	NA	SSA/SSB	Lung	NA	NA	NA
		NA	53	F	Dry eye, dry mouth	NA	SSA/SSB	Lung	NA	NA	NA
Kluka *et al* [20]	1	33	53	F	Dry eye, dry mouth	Monoclonal gammopathy	SSA/SSB	Lung	I	HCQ, GS	NA
Keszler *et al*[21]	1	60	62	F	Dry eye, dry mouth	RF	–	Minor labial salivary gland	I	–	Improved
Watanabe *et al*[22]	1	29	49	F	Dry eye, dry mouth	NA	SSA/SSB	Lung	IV	Chemotherapy	Improved
De Vita *et al*[23]	1	45	51	F	Dry eye, dry mouth	PGS, cryoglobulins, RF, low C4	SSA/SSB	Parotid gland	IE	RTX	Improved
Covelli *et al*[25]	2	32	35	F	Dry eye, dry mouth	PGS, RF, low C4	SSA	Parotid gland	NA	RTX	NA
		42	44	F	Dry eye, dry mouth	Monoclonal gammopathy, RF	SSA/SSB	Lung	NA	GS, RTX	NA
Ornetti *et al*[26]	1	73	73	F	Dry eye, dry mouth	PGS	SSA	Parotid gland	NA	RTX, chemotherapy	Improved
Movahed *et al*[27]	1	36	41	F	Dry mouth	PGS	NA	Submandibular glands	III	–	Improved
Zenone *et al*[28]	2	55	56	F	Dry eye, dry mouth	PGS, cryoglobulins, RF	–	Parotid gland	NA	RTX, chemotherapy,	Progressive

	31	42	F	Dry eye, dry mouth	PGS, cryoglobulins, Monoclonal gammopathy	SSA/SSB	Parotid gland	NA	radiotherapy HCQ, RTX	Improved

PGS: Parotid gland swelling; RF: Rheumatoid factor; RTX: Rituximab; GS: Glucocorticoids; HCQ: Hydroxychloroquine; NA: Not available; "-": Negative.

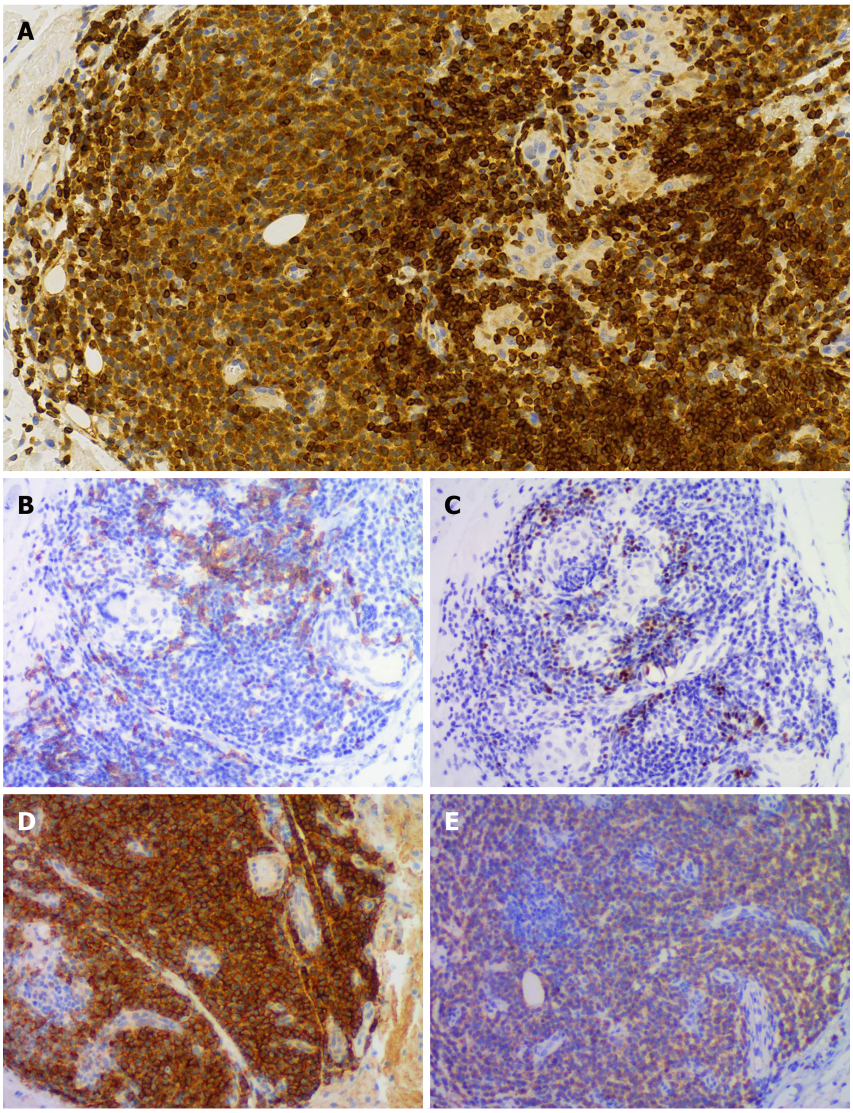

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Figure 3 Immunohistochemical staining. A-C: Small-sized B lymphocytes with a pale cytoplasm positive for Bcl2 (A), CD20 (B) and PAX5 (C); D and E: Plasma cells were highlighted by CD138 (D) and immunoreactive for an anti-Ak antibody (E).

lymphoma was increased in SS patients with salivary gland swelling and/or cryoglobulinemia. According to the reviewed literature, parotid gland swelling, positive RF, monoclonal gammopathy, and low C4 are more frequent (40%–85%) in SS patients with MALT lymphoma, while cryoglobulinemia and cryoglobulinemic vasculitis are less frequent (13%). However, none of these parameters was screened in our patient. This may have been because the MALT lymphoma involved skin rather than the parotid gland. Further prospective studies are required. Constant monitoring of lymphoma is necessary in SS patients.

Labial salivary gland biopsy is a diagnostic test for SS and aids in the detection of lymphoma. Cases of MALT lymphoma with SS in the labial salivary glands have rarely been reported. Keszler *et al*[21] reported a case of a 60-year-old female patient with SS who developed MALT lymphoma in the labial salivary glands during a 2-year time interval. In our case, labial salivary gland biopsy revealed lymphocytic infiltration and chronic inflammation (FS = 2) and showed no evidence of neoplastic cells.

An FS ≥ 3 was suggested as a predictive factor for lymphoma development[46]. However, negative FS (FS < 1) was present in five patients with MALT lymphoma in our literature review. Consistently, Haacke *et al*[10] showed that FS did not differ between SS patients with parotid MALT lymphoma and SS controls who were lymphoma free. The percentage of biopsies with FS ≥ 3 was even higher in the control group (36% *vs* 27%). Therefore, the FS of labial gland biopsies is not a predictive factor for SS-associated MALT lymphomas.

Pollard *et al*[24] reported the treatment of MALT lymphoma in SS, including watchful waiting, surgery, radiotherapy, surgery combined with radiotherapy, rituximab monotherapy, and rituximab combined with chemotherapy, and found that an initially high SS disease activity likely constitutes an adverse prognostic factor for the progression of lymphoma and/or SS. Such patients may require treatment for both conditions. In SS patients with localized asymptomatic MALT lymphoma and low SS disease activity, watchful waiting seems justified. In our case, the patient with low SS disease activity and localized asymptomatic MALT lymphoma received positive chemotherapy at her request.

CONCLUSION

Prompt recognition of the possible cutaneous lymphoproliferative complications of SS is essential to avoid delayed diagnosis or treatment. Further multicenter prospective studies are necessary to better understand the pathogenesis, treatment, and outcomes of MALT lymphoma in SS patients.

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FOOTNOTES

Author contributions: Liu Y performed all the literature review, clinical analysis, and wrote the manuscript with contributions from all authors; Zhu J and Huang YH designed and supervised the study; Zhu J, Zhang QR, Zhao LL and Yu RH revised the manuscript.

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ORCID number: Ying Liu 0000-0002-2066-5603; Jian Zhu 0000-0002-6244-9917; Yan-Hong Huang 0000-0002-0815-2741; Qian-Ru Zhang 0000-0002-2804-9768; Li-Ling Zhao 0000-0003-0631-9162; Ruo-Han Yu 0000-0002-6635-7649.

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