Extranodal Marginal Zone Lymphoma From Ocular Adnexae With Subcutaneous Involvement

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Abstract: Extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue usually originates from cutaneous or mucosal surfaces. A rare site of involvement is the subcutaneous tissue of any location. Here, we describe a 58-year-old man who presented with bilateral extranodal MZL of mucosa-associated lymphoid tissue from ocular adnexae that involved subcutaneous tissue and subsequently extended to multiple anatomical locations in the head and neck, upper back, and arm. The neoplastic cells expressed B-cell markers, and the plasma cells expressed IgG4. The unusual pattern of infiltration of this extranodal MZL and the possible significance of IgG4 expression in this case are discussed.

Key Words: MALT, lymphoma, extranodal, subcutaneous, ocular adnexa

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INTRODUCTION

Marginal zone lymphoma (MZL) is a B-cell lymphoma that accounts for 5% of all the cases of non-Hodgkin lymphoma and comprises 3 distinct subtypes: nodal, splenic, and extranodal. Extranodal MZL of mucosa-associated lymphoid tissue (MALT) usually arises in skin (the so-called "SALT") or mucosal surfaces of gastrointestinal tract, lungs, or upper respiratory tract; less frequent sites of involvement include thyroid, salivary glands, conjunctiva, and breast.[1] The disease is histologically confined to the mucosa and submucosa, or it focally infiltrates the underlying soft tissues, while subcutaneous involvement at diagnosis or at relapse is unusual.[2,3]

Primary extranodal MZL of the ocular adnexae is rare, and it is characterized by localized disease,[4,5] although bilateral involvement has been described in 10%–15% of the cases.[6] Recently, a subset of these cases has been associated with infection by *Chlamydia psittaci* in specific geographic areas.[5] The disease can be effectively controlled with radiotherapy. However, systemic relapses have been reported in approximately 20% of patients who initially presented with stage IE disease.[7]

In this report, we describe a patient with stage IE extranodal MZL of periorbital adnexae that subsequently developed subcutaneous involvement in distant sites. We also reviewed the literature to identify similar cases to determine the clinicopathologic features and hypothesize possible pathogenic mechanisms.

MATERIAL AND METHODS

The medical records of the Oncology Service at the Edgardo Rebagliati Martins National Hospital in Lima, Peru, were searched for extranodal MZL from ocular adnexa. This study was approved by the Institutional Review Board at the Edgardo Rebagliati Martins Hospital. The biopsy specimens were reviewed by 4 of the authors (D.M., P.Q., R.N.M., C.T.C.). Routine H&E stains were obtained, and immunohistochemical studies were performed on fixed paraffin-embedded tissue sections using antibodies against CD20 (Dako, Carpinteria, CA; dilution 1:100), CD3 (Dako; dilution 1:100), CD10 (Novocastra, Newcastle upon Tyne, UK; dilution 1:100), CD5 (Thermo Fisher, Fremont, CA; dilution 1:20), BCL-6 (Dako; dilution 1:10), BCL-2 (Leica Microsystems, Buffalo Grove, IL; dilution 1:200), cyclin D1 (Thermo Fisher; dilution 1:20), immunoglobulin kappa light chain (Dako; dilution 1:20,000), immunoglobulin lambda light chain (Dako; dilution 1:20,000), IgG (Dako; dilution 1:40,000), and IgG4 (Life Technologies, Grand Island, NY; dilution 1:150). Clinical data including age, sex, complete blood counts, Eastern Cooperative Oncology Group performance status, presence of B symptoms, laboratory values, therapy received, and response to therapy were gathered. For the systematic review, a literature search using the keywords *MALT* or *"marginal zone lymphoma"* and *"subcutaneous"* was performed using Pubmed through December 31, 2012. Pertinent clinical and pathological data were retrieved from cases meeting criteria for extranodal MZL of the ocular adnexa with either concurrent subcutaneous involvement at diagnosis or subcutaneous relapse. Data are reported using descriptive statistics.

CASE DESCRIPTION

A 58-year-old man with a previous diagnosis of malaria presented with a 7-year history of bilateral painless exophthalmos

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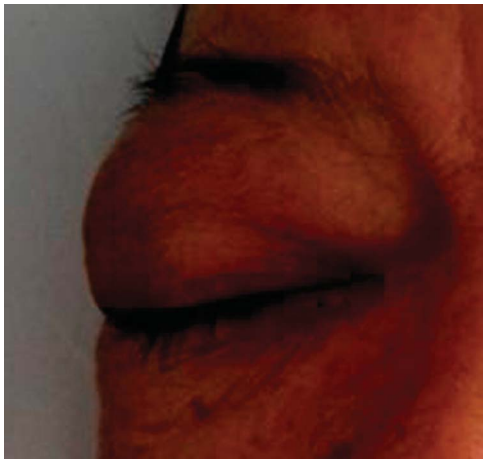

FIGURE 1. Initial clinical presentation of the patient. Asymptomatic exophthalmos is noted.

without B symptoms. A biopsy from orbital tissue was diagnosed as reactive changes without evidence of malignancy, 1 year after symptoms started. The exophthalmos progressed, and 6 years later, the patient noted the presence of multiple skin nodules in the trunk. Physical examination revealed an Eastern Cooperative Oncology Group performance status of 0, bilateral exophthalmos with the right, more prominent than the left side (Fig. 1). Examination of skin revealed multiple erythematous, nodular, and infiltrated lesions on the left frontoparietal and right parietal region, posterior neck, and upper back. In addition, a 5-cm erythematous exophytic tumor with regular border was identified on the left arm (Fig. 2). Bilateral cervical and supraclavicular lymph nodes, most of them larger than 2 cm in diameter were detected. A computed tomography scan with intravenous contrast revealed the presence of multiple cervical nodes and subcutaneous deposits in the head, neck, trunk, and left arm. Complete blood count showed hemoglobin 15.7 g/dL, leukocyte count 5.6×10^9 per liter, neutrophils 2.9×10^9 per liter, and platelets 196×10^9 per liter. The basic metabolic panel, liver function tests, lactate dehydrogenase, β-2–microglobulin, and serum protein electrophoresis were within the normal range. Serologic studies for human immunodeficiency virus, hepatitis B and C were negative.

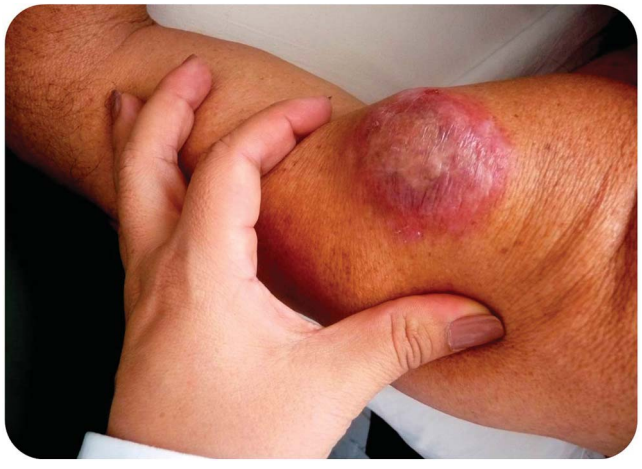

FIGURE 2. A few years later, the patient presented with multiple subcutaneous nodules. One on the left arm was particularly large and indurated.

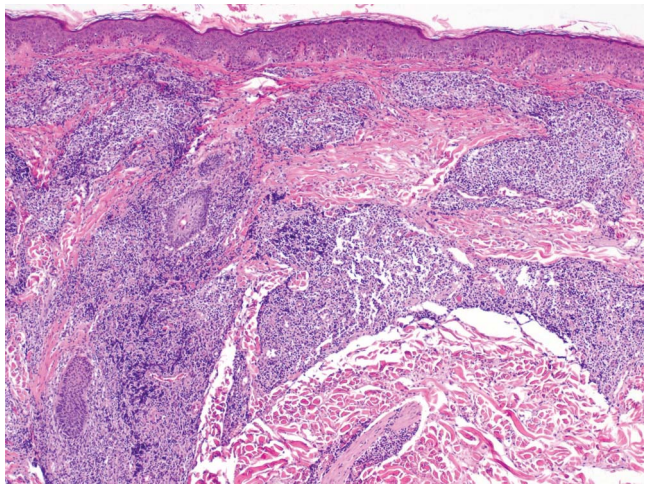

FIGURE 3. Periorbital skin biopsy. The sections revealed a dense superficial and deep perivascular and periadnexal infiltrate. Notice the grenz zone underlying epidermis and the lack of epidermotropism (H&E, ×4).

Serology studies for *C. psittaci*, *Chlamydia trachomatis*, and *Chlamydia pneumoniae* were negative. IgE level was 595 IU/mL (normal range, 0–99 IU/mL). Bone marrow aspirate revealed a normocellular marrow with trilineage hematopoiesis. The final diagnosis was stage IVA extranodal MZL arising from the ocular adnexae. The patient received 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with a complete radiological but partial clinical response. Patient is alive with disease at 9 months from diagnosis.

PATHOLOGICAL FINDINGS

A biopsy from the left periorbital skin revealed a dense nodular lymphocytic infiltrate involving superficial and deep dermis (Fig. 3). The infiltrate was composed of medium-sized lymphocytes with round to irregular nuclear contours. A

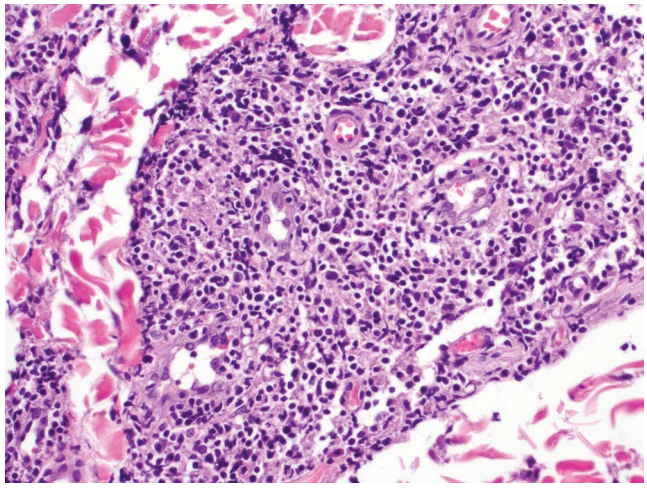

FIGURE 4. Periorbital skin biopsy. The infiltrate is composed of small- to medium-sized lymphocytes, plasma cells, and histiocytes. Lymphocytes with oval to round slightly irregular nuclei and a rim of cytoplasm (monocytoid) are seen (H&E, ×10).

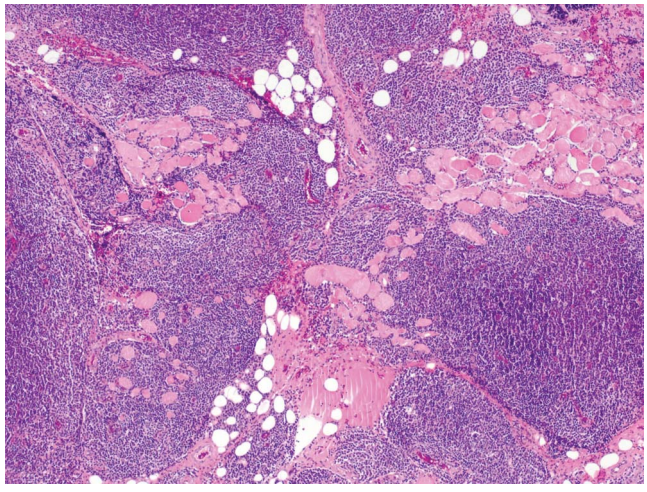

FIGURE 5. Orbit soft tissue biopsy. A very dense infiltrate composed of lymphocytes and numerous plasma cells dissecting muscle fibers and subcutaneous adipose tissue is seen. Rare residual germinal centers were also present (right-hand lower corner) (H&E, ×4).

subset of cells showed monocytoid morphology (Fig. 4). Histiocytes and numerous plasma cells were also present. A grenz zone was seen, and no epidermotropism was noted. A biopsy from the right orbit soft tissue revealed remnants of skeletal muscle, fibrous stroma, and a dense lymphocytic infiltrate with abundant plasma cells (Fig. 5). Immunohistochemical studies in both biopsies showed that most lymphocytes reacted with CD20 (Fig. 6). Reactive CD3-positive lymphocytes were present and estimated as 50% of the infiltrate. CD20-positive B lymphocytes were negative for CD5 and CD10. All lymphocytes were negative for cyclin D1. Remnants of germinal centers were strongly reactive with BCL6 and negative with BCL2. Most of the plasma cells were highlighted with anti-immunoglobulin kappa light chain (Fig. 7), and rare plasma cells reacted with lambda (Fig. 8), in a monotypic distribution. Similarly, numerous plasma cells were highlighted with IgG and were reactive with IgG4 (about 90% of the IgG-positive plasma cells were positive for IgG4; >50 plasma cells positive for IgG4 per high power field were counted; Fig. 9).

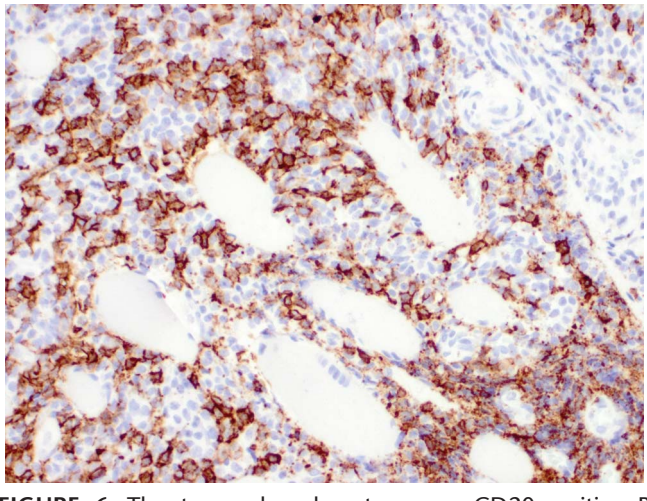

FIGURE 6. The tumor lymphocytes were CD20-positive B cells. The CD20-positive cells infiltrated muscle fibers and adipose tissue (CD20 immunohistochemical study, ×20).

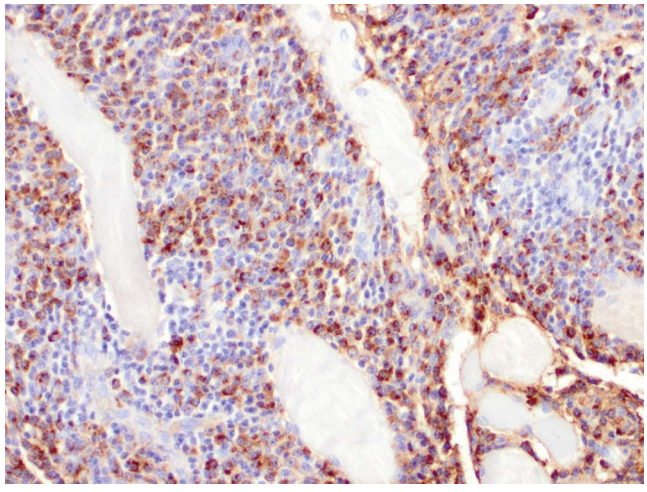

FIGURE 7. Abundant plasma cells expressing kappa light chain were identified (kappa light chain immunohistochemical study, ×20).

DISCUSSION

Extranodal MZL of the ocular adnexa is rare[7] and usually presents with localized disease.[4,5,8] Bilateral involvement of the orbit is an unusual presentation being reported in 10%–15% of the cases.[6] Only 15%–25% of patients present with stage IV disease.[9–11] Disseminated lesions and subcutaneous involvement by MALT lymphomas arising in ocular adnexae, as seen in this case, are therefore very rare events.[12]

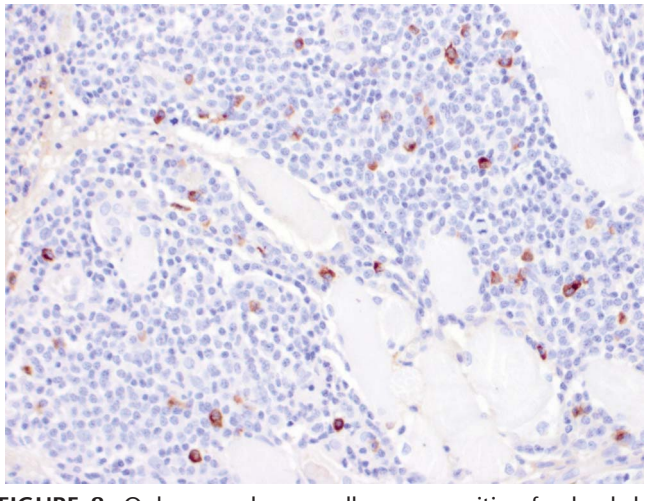

FIGURE 8. Only rare plasma cells were positive for lambda light chain. The kappa:lambda ratio was >10:1, supporting the monotypic nature of the plasma cells (lambda light chain immunohistochemical study, ×20).

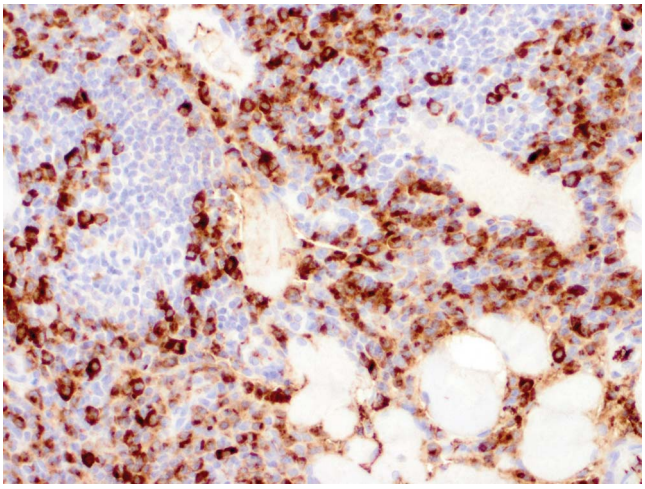

FIGURE 9. IgG4 was expressed by most of the plasma cells within the infiltrate (IgG4 immunohistochemical study, ×20).

A literature search was performed to identify case reports and series of patients with MALT lymphomas with synchronous or metachronous ocular and subcutaneous involvement. Our search rendered 39 articles, from which 2 articles[2,3] reported on 10 patients who met the above mentioned criteria (Table 1). Jonak et al[2] described 9 patients with extranodal MZL of the ocular adnexa and subcutaneous involvement. From the 11 cases with extranodal MZL of the ocular adnexa including our own case, 3 cases had a synchronous presentation, and 8 were metachronous. Four cases with a metachronous presentation experienced late relapses that occurred as late as 40 months from diagnosis.

MALT lymphomas have been frequently associated with chronic infectious agents such as *Helicobacter pylori* in the case of gastric lymphomas, *Borrelia burgdorferi* in cutaneous sites, and *C. psittaci* in the case of orbital MALT lymphoma. Supporting chronic antigenic stimulation as a potential etiology, most of the cases described by Jonak et al[2] had associated autoimmune disorders such as Sjogren syndrome and rheumatoid arthritis. Vincenti et al[3] described a case of extranodal MZL of the ocular adnexae and subcutaneous involvement in association with chronic HCV infection. In our case, the only relevant history was malarial infection in 3 separate times.

Recently, an association between IgG4 sclerosing disease and lymphoproliferative disorders including MZL has been described. IgG4 sclerosing disease usually presents with multiple benign masses in middle-aged or elderly men. Although the pathogenesis of IgG4 sclerosing disease is unknown, it is believed to be autoimmune. A few cases of MALT lymphoma with abundant IgG4-positive monotypic

TABLE 1. Cases of MALT Extranodal MZL Involving the Ocular Adnexae and Subcutaneous Tissue Reported in the Literature

Case	Author	Sex	Age	Primary	Initial Treatment	Method Detection
1	Jonak et al[2]	F	58	Orbit	Radiotherapy	CT
2	Jonak et al[2]	F	61	Orbit	Radiotherapy	CT
3	Jonak et al[2]	F	64	Conjunctiva	Radiotherapy	CT
4	Jonak et al[2]	F	49	Orbit	Radiotherapy	PET-CT
5	Jonak et al[2]	F	77	Lacrimal gland	Radiotherapy	PET-CT
6	Jonak et al[2]	F	71	Orbit	CHOP	Self-assessment
7	Jonak et al[2]	F	84	Orbit, cervical node	Radiotherapy, MCP	CT
8	Jonak et al[2]	M	80	Lacrimal gland	Radiotherapy	Self-assessment
9	Jonak et al[2]	M	85	Conjunctiva	Radiotherapy	CT
10	Vincenti et al[3]	M	51	Orbit, mediastinal, abdominal LAD, bone marrow	Pegylated Interferon, ribavirin	Self-assessment, PET-CT
11	Beltran et al[13]	M	58	Orbit, cervical node	R-CHOP	CT, self-assessment

Case	Subcutaneous Involvement	Subcutaneous Localization	Treatment	Follow-up	Survival (mo)
1	Metachronous	Gluteal	Bortezomib	Alive	204
2	Metachronous	Suprapubic	CHOP	Alive	244
3	Metachronous	Lower back	R-CHOP	Alive	195
4	Synchronous	Gluteal	Radiotherapy	Alive	8
5	Metachronous	Periumbilical, paravertebral, lower back	R-CHOP, watchful waiting	Dead (heart disease)	137
6	Metachronous	Forearm	R-CHOP	Alive	93
7	Metachronous	Occipital	Radiotherapy	Dead (heart disease)	26
8	Metachronous	Face	CHOP	Dead (heart disease)	11
9	Metachronous	Lower back	Watchful waiting	Dead (senility)	49
10	Synchronous	Neck, forearm, back, pectoral region, cheekbones	Pegylated Interferon, ribavirin	Alive	19
11	Synchronous	Arm, cervical, frontoparietal, parietal, upper back	R-CHOP	Alive	9

LAD, lymphadenopathy, PET-CT, positron emission tomography–computed tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

plasma cells are suspected to arise from IgG4 sclerosing disease.[13–15] However, a recent report found a high percentage (39%) of primary cutaneous MZLs to have IgG4 expression, while from 120 noncutaneous MALT lymphomas, only one case, located in the ocular adnexae, expressed IgG4.[16] None of the reported cases had evidence of an associated IgG4-related disease. In our case, we identified more than 50 plasma cells per high power field expressing IgG4, raising the suspicion of an underlying IgG4 sclerosing disease. In support of this possibility, our case had several cutaneous and subcutaneous lesions, predominantly in the head, neck, back, and arms. Most of the previously reported cases of IgG4 sclerosing disease in skin, however, have been described as solitary lesions located in the lower back or gluteal areas.[2] Similar to our case, Vincenti et al[3] reported a case with multiple skin nodules located in the forearm, back, cheekbones, parotid glands, and right pectoral region; the patient also had HCV infection, and a complete remission was obtained with ribavirin and pegylated interferon. Our patient was negative for HCV.

It may be postulated that the unusual pattern of dissemination seen in our patient is related to similarities between ocular adnexae and subcutaneous adipose tissue in terms of homing environment, perhaps explained by a common embryological origin from the ectoderm. In any case, despite dissemination, MALT lymphomas with either skin or orbital involvement seem to be associated with an excellent prognosis.[1] A review of the literature shows that with a 49-month median follow-up, 7 out 11 (64%) patients were alive at the time of reports, and the other 4 (36%) died from other causes.

In summary, herein we present a case of marginal zone MALT lymphoma with plasmacytic differentiation with bilateral involvement of the orbit and multiple subcutaneous lesions. A review of the literature reveals that similar cases carry an indolent course. The numerous monotypic plasma cells expressing IgG4 present in our case suggest either an association with IgG4 sclerosing disease or a similar pathogenesis to primary cutaneous MZLs, recently reported to have frequent IgG4 expression. The association between IgG4-expressing MZLs (primary cutaneous or from ocular adnexae) and IgG4 sclerosing disease still needs to be elucidated.

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