

# Same Disease, Different Approaches: A Report on Six Lymphoma Cases with Extranodal Marginal Zones in Rare Sites

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**ABSTRACT** Marginal zone lymphoma (MZL) is a heterogeneous disease with the most common form being extranodal marginal zone lymphoma (EMZL). It mostly involves the glandular epithelial surfaces such as the stomach, ocular adnexa, lacrimal and salivary glands, thyroid, breast, and lungs. Gastric and ocular adnexal EMZL are related to specific infectious agents and can be treated with antibiotics especially during the early stages. Surgery, radiotherapy, rituximab, rituximab with chemotherapy, and observation are the other approaches available for the treatment of EMZL. Here, we presented several cases of EMZL with varying stages of involvements of rather extraordinary tissues along with our systemic treatment approaches. Additionally, we have also described the successful implementation of local treatment options.

**Keywords:** Marginal zone lymphoma; rituximab; extranodal

Marginal zone lymphomas (MZL) constitute around 10% of non-Hodgkins lymphomas. Extranodal marginal zone lymphoma (EMZL) is the most common form of MZL, constituting more than 70% of all MZL cases.<sup>1</sup> Marginal zone lymphoma can be considered as a prototype of an antigen-driven tumor and has many microorganisms and autoimmune diseases associated with its pathogenesis.<sup>2</sup> A pooled analysis of a series of trials showed that Sjögren's Syndrome could increase the risk of MZL and EMZL of the parotid gland to 30 and 1000-folds, respectively. A similar association was also reported with systemic lupus erythematosus.<sup>3</sup> The main causative infectious agents of the EMZL that were also associated with the specific disease locations were *Helicobacter pylori*, *Chlamydia psittaci*, *Campylobacter jejuni*, *Borrelia burgdorferi*, and *Achromobacter xylosoxidans*.<sup>4</sup>

The EMZL is diagnosed by the pathological examination of the biopsy, usually showing the centrocyte-like and monocytoid-like B cells from the marginal zone.<sup>5</sup> The Flow-cytometry analysis for extranodal marginal zone lymphomas was positive for

CD19, CD20, CD79a, CD22, and cell surface Ig but negative for CD5, CD10, CD23, and Cyclin D1. This feature is important for a differential diagnosis.<sup>6</sup> After diagnosis, staging procedures such as computed tomography (CT), positron emission tomography (PET), endoscopy, and Endosonography (for gastric EMZL only) are performed according to the underlying primary site and accompanying symptoms. Although most cases are presented during their early stages (stages IE and IIE), only a complete staging evaluation can reveal the widespread of the disease in almost half of the cases.<sup>7</sup> MALT-IPI score was used to identify the prognosis.

Treatment decisions are driven by the primary site and extent of involvement. While local treatments such as surgery and radiotherapy are preferred during the early stages, systemic chemotherapy with or without immunotherapy (rituximab) is the treatment of choice during the later stages. However, randomized trials are lacking, and the recommendations are generally from the case series and the subgroup analyses of the non-Hodgkins lymphoma trials.<sup>8</sup>

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Here, we presented several cases of EMZL with varying stages of involvements of rather extraordinary tissues along with our systemic treatment approaches. Additionally, the successful implementation of local treatment options is also described (Table 1).

## CASES

### CASE 1

A 71-year-old female patient was presented to the hospital with a mass on the kidney. She was diagnosed with EMZL upon the pathological examination of the radical nephrectomy material. The Ki-67 proliferation index was relatively low. Hepatic, gastric, and diffuse mediastinal involvement was detected using PET-CT with no B symptoms. The patient was at stage 4A EMZL, and her Eastern Cooperative Oncology Group (ECOG) performance status was 1. The patient was administered rituximab intravenously every week for four cycles. Six months later, disease progression was detected upon examination. Rituximab plus bendamustine chemotherapy regimen was administered for six cycles, and the patient was in complete remission in the six years of follow-up.

### CASE 2

A 59-year-old female patient had undergone a sub-mandibular lymph node excision in 2001. The pathological examination revealed it as the mucosa-associated lymphoid tissue lymphoma (MALT lymphoma). She was followed-up without any adjuvant therapy due to her stage 1E disease. In January 2005, a right ocular mass appeared, and an excisional biopsy

was performed. In the imaging studies, no residual disease was found with any evidence of involvement. The pathological diagnosis was EMZL. The patient was followed up without adjuvant treatment.

In May 2011, the patient suffered from a mass in the left lacrimal gland. An excisional biopsy was performed, and small monocytoid lymphoid cells were observed with diffused growth patterns. Immunohistochemically, they were stained positive for CD20 but negative for CD23. The results were consistent with EMZL diagnosis, and even in this recurrence, the stage of the disease was found to be 1E. Six cycles of rituximab plus cyclophosphamide, vincristine, and prednisolone (R-CVP) were administered to the patient every 21 days due to multiple recurrences. A complete response was attained, and the patient is in complete remission in a follow-up since February 2012.

### CASE 3

A 44-year-old male patient complaining of back pain was presented to the clinic in February 2017. He also had a cough, hoarseness, and mild fever. Due to the lack of response to multiple courses of antibiotic therapy, fiberoptic bronchoscopy was performed. Finally, a pulmonary core biopsy was carried out, and the diagnosis of MZL was revealed. Since the patient had a solitary lesion in the lung, he underwent lower lobectomy of the right lung and lymph node dissection. Surgery revealed a neoplasm measuring 4.5x4.5x2 cm. Immunohistochemically, CD20 and Bcl-2 were found to be diffuse positive, while CD10, CD30, Cyclin D1, TTF-1, and Cam 5.2 were found to be negative. No lymphoma involvement was detected

TABLE 1: Clinical characteristics of the patients.

Case No	Sex	Location	MALT-IPI		Treatment	Response to Treatment	Recent Disease Status
			Stage	Score			
1	F	Kidney	4	2	R	CR with R; CR with R-Bendamustine	Disease-free on follow-up
2	F	Lacrimal Gland	1E	1	R-CVP	CR	Disease-free on follow-up
3	M	Lung	1E	0	Surgery	CR	Disease-free on follow-up
4	F	Lung	1E	0	Radiotherapy	CR	Disease-free on follow-up
5	M	Nodal, Splenic, Pulmonary, and Gastric	4	2	R-Bendamustine	PR	On Treatment
6	M	Retroperitoneal Soft Tissue	1E	0	Radiotherapy	CR	Disease-free on follow-up

F: Female; M: Male; R: Rituximab, R-CVP: Rituximab, Cyclophosphamide, Vincristine, Prednisolone

in the dissected lymph nodes, and the patient showed complete remission in the follow-ups.

#### CASE 4

Upon the examination of a 67-year-old female, a left lung mass was detected with CT, for which she underwent a lung core biopsy. The pathologic diagnosis was EMZL with no B symptoms. The PET-CT examination revealed a lesion, where the largest diameter was 27x25 mm with a ground-glass opacity around it. The patient was consulted with radiation oncology, and radiotherapy was given to the patient for 15 days with a total dose of 3060 cGy. The patient is still in complete remission in the tenth year of follow-up.

#### CASE 5

A 53-year-old male patient was presented to a physician with a non-healing cough. The thorax CT examination revealed widespread parenchymal consolidations, multiple mediastinal lymph nodes, a subcarinal lymph node of 12 mm diameter, and left hilar lymph nodes. The transthoracic core biopsy showed a low-grade B cell lymphoma consistent with EMZL. Hence, the patient was staged with PET-CT. Metabolic active disease was observed in mediastinal lymph nodes, lung, spleen, intraabdominal lymph nodes, and fundus of the stomach. The patient had ischemic heart disease with a cardiac pacemaker, and his ECOG performance status was 1. Therefore, a rituximab plus bendamustine chemotherapy regimen was administered to the patient for six cycles every 28 days. After all the treatment courses, the final assessment showed a partial response. Hence, an additional three cycles of the same regimen were administered. After six cycles of rituximab plus bendamustine, complete remission was obtained, and even at the first follow-up after three months, the patient was in remission.

#### CASE 6

A 63-year-old male patient was presented to our clinic for a 2.5 cm mass, which was behind the left kidney and was noticed incidentally. The lesion was then sampled by core biopsy. The pathological diagnosis was EMZL. No other involvement was observed in the PET-CT. Due to the staging results, the patient was administered definitive involved-field ra-

diotherapy in 17 fractions with a total dose of 3060 cGy. The patient is doing well and is in complete remission.

#### ETHICAL STATEMENT

The local ethics committee approved the study, and due to the retrospective nature of the disease, the need for informed consent was waived.

#### DISCUSSION

EMZL appears in gastric and non-gastric forms and is generally detected during early stages, but in 30 percent of patients, it may also involve the bone marrow, lymph nodes, and other mucosa-associated sites.<sup>9</sup> Particularly, patients presented with the extranodal disease accompanied by disseminated nodal involvement were considered to have NMZL even in the presence of splenic involvement. In contrast, the term 'EMZL' was favored in the case of an extranodal predominant disease with localized nodal involvement.<sup>10</sup> In the fifth case, the patient was presented with EMZL in the nodal, splenic, pulmonary, and gastric locations concomitantly, which is a rare presentation. This patient had an advanced stage disease, which was not relevant for local treatment options. Thus, he was treated successfully using a combination of anti-CD20 monoclonal antibody rituximab and an alkylating agent bendamustine.

In advanced-stage disease, the available treatment options are rituximab with or without chemotherapy, targeted therapies, and hematopoietic stem cell transplantation.<sup>8</sup> In phase 3 non-inferiority trial, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), used as the standard chemotherapy regimen for advanced indolent lymphomas during that period, were compared to the R-Bendamustine (RB). The median follow-up time of 45 months progression-free survival (PFS) was significantly higher in the RB group (69.5 vs. 31.2 months, respectively,  $p < 0.0001$ . [H=0.58, 95% CI 0.44-0.74]). Only erythematous skin reactions were found to be significantly higher in the RB group.<sup>11</sup> In the BRIGHT study, RB was compared with R-CHOP and R-CVP treatments for non-inferiority. The complete response rates as the primary endpoint for BR and R-CHOP/R-CVP arms were 31% and 25%, respectively ( $p=0.0225$  for non-inferior-

ity). The overall response rate for BR was 97% and 91% for R-CHOP/R-CVP ( $p=0.0102$ ). All of the adverse events were significantly higher in the R-CHOP/R-CVP arm except for vomiting and drug hypersensitivity reactions.<sup>12</sup> We preferred the RB regimen for our patient due to his cardiac comorbidities. After six cycles of the treatment regimen, imaging studies showed a partial response, and we decided to administer three more cycles of chemotherapy. The patient tolerated the chemotherapy well with an uneventful course.

Local treatment options included radiotherapy and surgery, but some investigators did not prefer the latter option. Probable loss of pulmonary function was the main concern regarding surgery in the pulmonary EMZL.<sup>13-15</sup> The superiority of chemotherapy was also supported by several studies making the role of surgery even more debatable.<sup>15,16</sup> We proceeded with surgery in case 3 due to isolated pulmonary involvement. The patient underwent lobectomy and lymph node dissection. However, there were different considerations about whether the true surgical procedure was lobectomy with lymph node dissection. Lee et al. analyzed the data of 39 patients diagnosed with pulmonary EMZL. Thirty (76.9%) patients underwent surgery, where eight of them had centrally located lesions while twenty-two patients had peripherally located lesions. All the patients with central lesions were treated with video-assisted thoracoscopic surgery (VATS). On the other hand, about one-third of the patients with peripheral tumors were treated with VATS, while two-thirds of them were treated with limited resection procedures such as VATS wedge resection and VATS wedge segmentectomy. According to the analysis, patients with peripheral lesions did not experience recurrence, but one of those with central lesions had a recurrence and further underwent a VATS lobectomy.<sup>17</sup> Overall, surgery was mainly used only to obtain relevant tissue for diagnosis. However, it could be performed with curative intent under convenient clinical conditions.<sup>18</sup>

Tsang et al. investigated the results of radiotherapy in 70 patients who had stage 1E and stage 2E EMZL. Disease localizations were found to be very diverse and included the stomach, orbital adnexa, salivary glands, thyroid, lungs, upper airways, urinary bladder, breast, and rectum. The administered median radio-

therapy dose was 30 Gy. The five-year disease-free survival (DFS) and overall survival rate was 76% and 96%, respectively. According to the analysis, localized EMZL patients had favorable survival outcomes with a moderate-dose of radiotherapy.<sup>19</sup> Our fourth case had a left lung nodule of approximately 2 cm in size and received a total of 3060 cGy radiation dose at 15 fractions. The patient is being followed-up in an uneventful course without any toxicities. Two of our pulmonary EMZL patients, who were treated with separate modalities, are also on follow-up and in remission.

In our retrospective analysis of 70 patients with stage 1E and 2E disease at a single institution, a 99% complete remission rate was achieved. The recurrence rate was 17 percent and was seen in the contralateral organ or distant sites.<sup>20</sup> Case 2 had submandibular primary NMZL and lacrimal gland EMZL in chronological order. About six years later, this patient had a contralateral recurrent mass as the cases described by Tsang RW. In the Tsang RW study, the recurrent cases were managed with local treatments, where the control rate was 95%.<sup>20</sup> We also performed excision during our patient's first recurrence diagnosed as lacrimal gland EMZL while for the third recurrence, we administered systemic chemotherapy rather than giving only local treatment, unlike before.

EMZL involves glandular mucosal surfaces, where antigenic stimulation leads to B cell irritation and proliferation.<sup>21</sup> The sixth patient was diagnosed with EMZL in retroperitoneal soft tissue, which was an extraordinary location. To our best knowledge, this is the first EMZL case that involves the retroperitoneal soft tissue. We treated our patient with involved-field radiotherapy in 17 fractions with a total dose of 3060 cGy without any significant toxicity, and the patient is being followed-up in complete remission.

Pelstring and Parveen reported that EMZL could also involve the kidney, uncommonly.<sup>22,23</sup> Recently, Garcia et al. also reported ten MZL cases involving the kidney. They only performed nephrectomy on three patients, and all of them are alive, where one of the patients was administered chemotherapy after nephrectomy. The other eight patients are found to be disease-free in the follow-ups.<sup>24</sup> Our first case with the extrarenal disease also underwent radical nephrectomy and was administered for four cycles of rituximab weekly.

In conclusion, EMZL places itself in a wide clinical spectrum. The disease could occur or recur at unusual locations involving nodal, splenic, and extranodal sites. Also, the first presentation can be observed at the nodal sites, or recurrences can be seen in the extranodal sites. These unusual presentations could be treated with noninvasive procedures such as radiotherapy, and for advanced stages, efficacious chemotherapeutic agents can be used. Although not present in our cases, the EMZL commonly occurs in patients with chronic infections or inflammatory disorders, which could further complicate the management. A wide-scale study with different disease states could clarify the optimal management of these patients.

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### Conflict of Interest

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### Authorship Contributions

*All authors contributed equally while this study preparing.*

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