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Original Article

Primary extranodal marginal zone lymphoma of the endometrium: report of four cases and review of literature

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Abstract: Primary extranodal marginal zone lymphoma of the endometrium (PEMZL-EM) is exceedingly rare and has not been well characterized. Herein, we study the clinicopathological, cytogenetic and molecular features of four cases, the largest case series reported to date. The median age of the four patients was 59 years. Clinical presentations included abnormal vaginal bleeding (three cases) and incidental finding (one case). There were no constitutional symptoms in any of the cases. None of the patients had evidence of lymphoma in any other anatomic sites including bone marrow. Histologically, the lymphoma was characterized by a nodular proliferation of small lymphocytes admixed with occasional immunoblasts and variable number of plasma cells, which was restricted to the endometrium in most cases. Lymphoepithelial lesions were not identified in any of the cases. All cases displayed the immunophenotype of marginal zone B-cell lymphoma. Cytogenetics and FISH studies revealed absence of characteristic chromosomal translocations. Molecular analysis demonstrated immunoglobulin heavy chain gene rearrangement in all cases, two of which were found to use IgVH3-30 gene by DNA sequencing. Three of the four patients were still alive after a median follow-up of three years. PEMZL-EM predominantly affects postmenopausal women and is characterized by distinct histological patterns, lack of specific genomic alterations, and indolent clinical course.

Keywords: Uterine lymphoma, marginal zone lymphoma, primary extranodal marginal zone lymphoma of the endometrium

Introduction

Approximately 25% of non-Hodgkin lymphomas (NHL) arise in extra-nodal sites [1, 2]. Extranodal marginal zone B-cell lymphoma (EMZL) constitutes approximately 7-8% of NHL and is often associated with chronic infections and underlying autoimmune diseases [3]. Studies have suggested that chronic antigenic stimulation may play an important role in its pathogenesis [3].

Primary lymphomas of the female genital tract are rare, accounting for approximately 2% of all extra-nodal lymphomas and less than 0.5% of the gynecologic malignancies [3, 4]. Uterine cervix is the most common site and uterine corpus involvement is very rare. The most common subtype is diffuse large B-cell lymphoma followed by follicular lymphoma [4]. Primary extranodal marginal zone lymphoma of the endometrium (PEMZL-EM) is exceedingly rare and to the best of our knowledge, only nine cases have been described as single case report in English literature [5-13]. Due to its low incidence, PEMZL-EM has not been well characterized and its etiology and pathogenesis are still unknown. In this study, we present four cases of PEMZL-EM, which is the largest case series ever reported, and characterize their clinicopathological, genetic and molecular features. We have also included a literature review of all the reported cases.

Material and methods

Case selection

This study was approved by the Institutional Review Board of North Shore-Long Island

Table 1. Clinical and laboratory findings of four cases of PEMZL-EM

Cases	No1	No2	No3	No4
Age	58	59	46	72
Clinical history	Colonic Ca	Hepatitis C	No	No
Presentation	Incidental finding	Vaginal bleeding; leiomyoma	Vaginal bleeding	Foul smelling bloody discharge
Specimen	Hysterectomy	Hysterectomy; EMC	Hysterectomy; EMC	EMC, ECC
White blood cell	N/A	8.7	6	9.8
Hemoglobin	N/A	13.2	12.2	13
Platelet	N/A	209	201	307
Lymphadenopathy	No	No	No	No
Site of involvement	EM	EM LFT (focal)	EM	EM, sMM
Histology				
Lymphoid infiltrate	Nodular	Extensive nodular	Nodular	Extensive nodular
LEL	-	-	-	-
Residual GC	-	-	+	-
BM Involvement	N/A	No	N/A	No
Immunophenotype				
Surface Igs	N/A	Kappa	Kappa	Lambda*
CD20	+	+	+	+
CD5	-	-	-	-
CD10	-	-	-	-
CD79A	+	+	+	+
CD43	+	-	-	+
cyclinD1	-	-	-	-
Ki-67	< 5%	< 5%	< 5%	< 5%
IGHV	Clonal N/A	Clonal IgVH3-30	Clonal N/A	Clonal IgVH3-30
Treatment	No	No	No	No
Follow-up	2 yrs	2 yrs	4 yrs	5 yrs
Status	Died of colonic carcinoma	Alive	Alive	Alive

Abbreviations: Ca, carcinoma; EMC, endometrial curettage; ECC, endocervical curettage; EM, endometrium; sMM, superficial myometrium; LEL, lymphoepithelial lesion; LFT, left fallopian tube; GC, germinal center; N/A, not available; BM, bone marrow. *Bone marrow.

Jewish Health system. Four cases of PEMZL-EM were identified from the files of the Department of Pathology at North Shore-LIJ Health System between 1998 and 2013. Cases were considered as primary lymphomas of the endometrium only if they met the following criteria [14]: (1) At the time of initial diagnosis, the lymphoma was primarily confined to uterine cavity and extensive work up did not reveal evidence of lymphoma in any other sites; (2) There was no evidence of leukemic phase; (3) There was a fairly long interval between the appearance of primary lymphoma and secondary involvement.

Histology and immunohistochemistry

Paraffin-embedded tissue was available from the diagnostic samples. Immunohistochemistry studies were performed with a panel of prediluted antibodies including CD3, CD5, CD10, CD20, CD23, CD43, CD79a, ki-67 (Ventana, AZ, USA); BCL-6, Cyclin D1 (Dako, CA, USA); BCL-2 (Zymed, CA, USA). Staining was performed using automated immunostainer (Ventana Medical System, Tucson, AZ, USA).

Flow cytometry

Single cell suspension was prepared from the fresh tissue. Cells were stained with a panel of fluorescence labeled monoclonal antibodies including CD3, CD4, CD5, CD7, CD8, CD10, CD19, CD20, CD23, FMC 7 (Becton-Dickenson Biosciences, San Jose, California). The cells were washed with PBS for three times and fixed in 4% paraformadehyde PBS solution before analysis. Routine three-color flow cytometric analysis was performed using FACSDiva software (Becton-Dickenson Biosciences, San Jose, California).

Cytogenetics and FISH studies

Conventional karyotying was performed following the standard protocols. Interphase fluorescence in situ hybridization (FISH) analysis was performed on either tissue imprints or paraffin-embedded tissue sections using LSI dual-color,

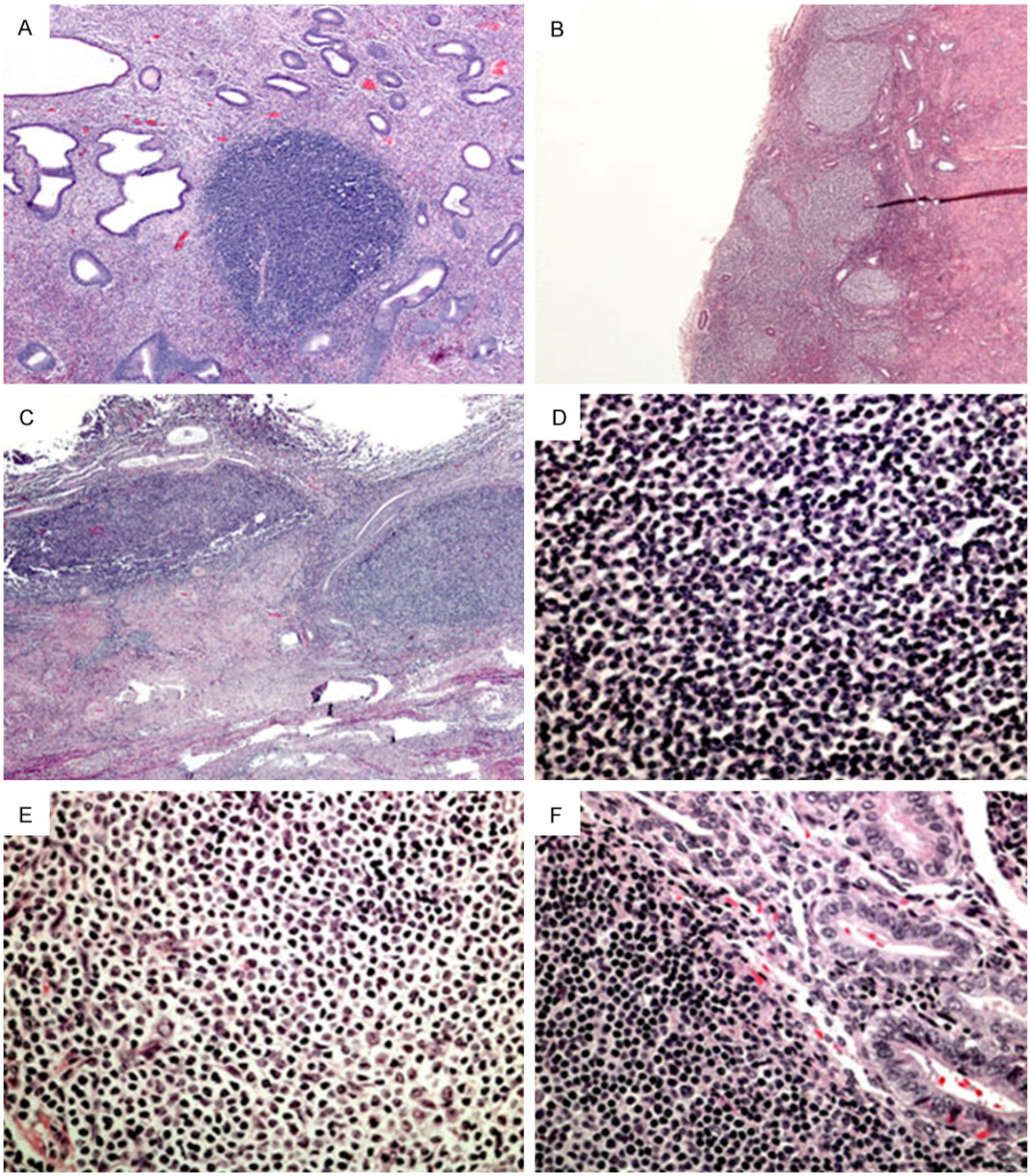

Figure 1. Histological features of the PEMZL-EM. A. Case 3 (× 40); B. Case 1 (× 20); C. Case 2 (×40); D. Small lymphocytes with scant cytoplasm and irregular nuclei (× 400). E. Small lymphocytes with monocytoid appearance (400); F. Lymphoepithelial lesions are absent (× 400).

dual-fusion translocation probes (API2/MALT1 t(11;18) (q21;q21), IGH/MALT1 t(14;18) (q32; q21), and IGH/BCL2 (Abbott Molecular, Des Plains, IL) following the standard protocol.

Molecular studies

Genomic DNAs were prepared from paraffin-embedded tissue sections using QIAamp DNA FFPE Tissue Kit (QIAGEN Inc., Valencia CA) The quality of DNA samples was assessed using the BIOMED-2 specimen control reaction and all samples yielded control gene PCR products ≥ 300 bp. PCR amplifications were performed in duplicate with commercial BIOMED-2 assays (InVivoScribe Technologies, San Diego, CA, USA). The reactions included three targeting

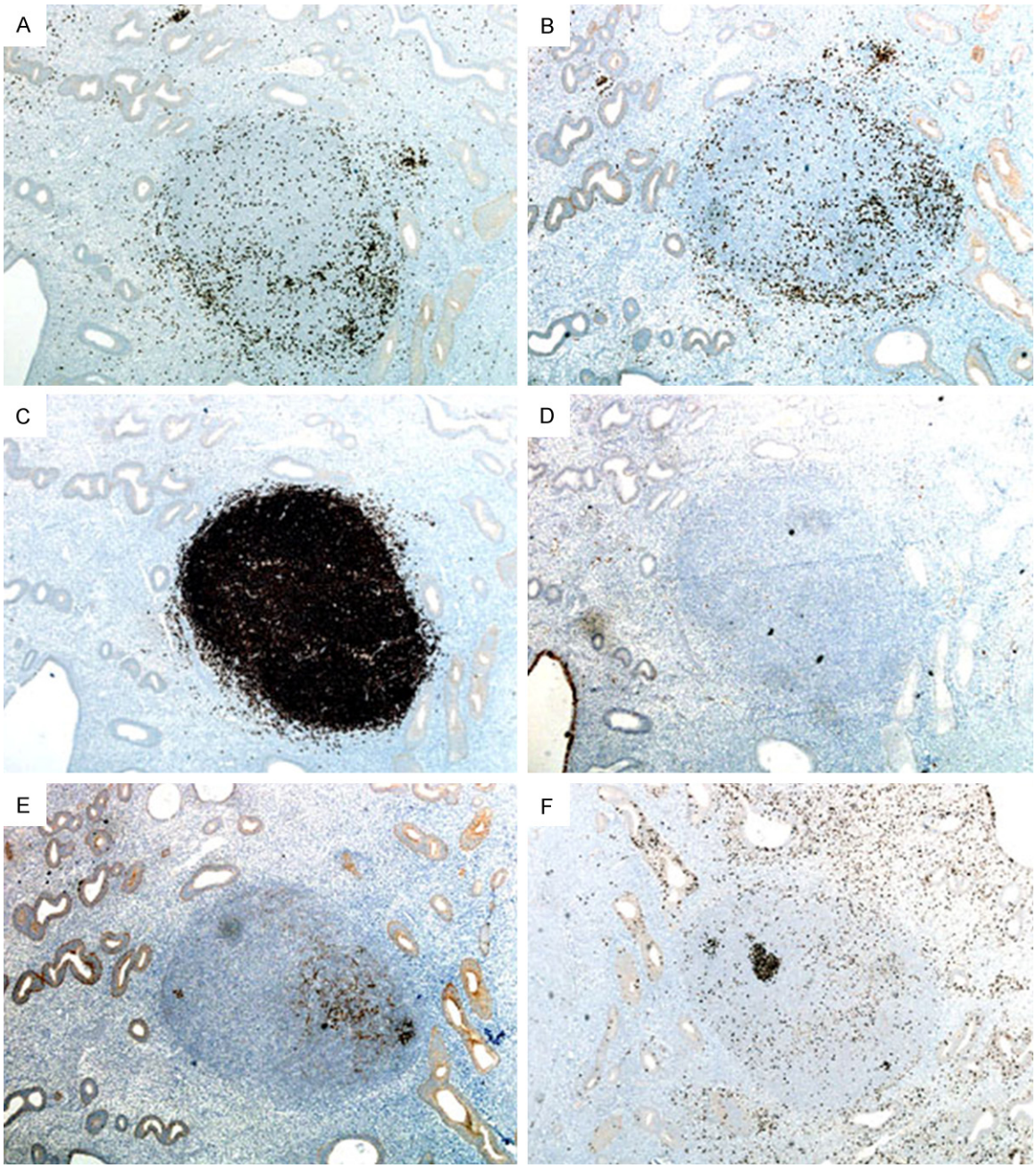

Figure 2. Representative immunohistochemistry in PEMZ-EM. A. CD3; B. CD5; C. CD20; D. cyclinD1; E. CD23; F. ki-67.

IGH (*IGH*$_A$: FR1 (variable region framework 1)-J; *IGH*$_B$: FR2-J; *IGH*$_C$: FR3-J), two targeting *IGK* (*IGK*$_A$: V-J; *IGK*$_B$: V-K$_{de}$ and JC intron-K$_{de}$) and one for *IGL*(V-J) [20]. The PCR products from *IGH* reactions were excised from agarose gel, purified using QIAquick Gel Extraction Kit (QIAGEN Inc., Valencia CA), and submitted for sanger sequencing using the common JH primer. DNA sequence analysis was carried out using IgBLAST program of National Center for Biotechnology Information.

Results

Clinical features

Table 1 summarizes the clinical and laboratory findings of our cases. This study included four patients, with a median age of 59 years at the

time of initial diagnosis (range 46 to 72 years). Three patients presented with abnormal vaginal bleeding and the lymphoma was an incidental finding in one patient. None of the patients had constitutional symptoms at the time of initial presentation. Other significant clinical findings included colonic adenocarcinoma (case one) and hepatitis C infection (case two). There was no known history of *Chlamydia psittaci* infection in all cases. Extensive work-up did not reveal any evidence of lymphoma in other anatomic sites. Complete blood count was normal in three cases with available information and none of the patients had lymphocytosis. The information for bone marrow staging was available in two cases, which showed no evidence of lymphoma by morphologic examination or immunohistochemistry. All cases had Ann Arbor stage IE disease and none of the patients received treatment for lymphoma. After a median follow-up of three years, three patients were still alive without disease progression and one died of unrelated malignancy two years after the diagnosis.

Histology and immunohistochemistry

Endometrial curettage and/or hysterectomy specimens were received for evaluation, which showed similar histological features in all cases. Microscopically, the endometrium was infiltrated by lymphoid nodules composed of a monotonous population of small to medium-sized lymphocytes (**Figure 1A-C**). In some cases the lymphocytes had scant cytoplasm and slightly irregular nuclei with inconspicuous nucleoli (**Figure 1D**), while in others they had clear cytoplasm, imparting a monocytoid appearance (**Figure 1E**). Immunoblasts were seen scattered throughout the infiltrate. Plasma cells were scarce in all but one case in which singly or small clusters of plasma cells were found at the periphery of the lymphoid nodules. Lymphoepithelial lesions were not seen in any of the cases (**Figure 1F**). Rare small residual germinal centers were noted within the lymphoid nodules in one case. The lymphoma was restricted to the endometrium in three cases and invaded the superficial myometrium in one case. However, no evidence of cervical involvement was found in any of the cases. There was focal mild monotonous lymphoid infiltration in one fallopian tube in case 2, raising suspicion (albeit not diagnostic) for minimal involvement by lymphoma. The endometrium was atrophic in three cases and proliferative in one case.

Immunohistochemistry (**Figure 2A-F**) demonstrated that the neoplastic cells were positive for CD20, CD79a and BCL-2; negative for CD5, CD10, CD23, BCL-6 and cyclinD1. Two cases were also CD43 positive. CD23 highlighted the remnants of follicular dendritic meshworks within the lymphoid nodules in one case. A small number of reactive CD3 positive T-cells were present in the background. All cases showed low proliferation index (less than 5%) as demonstrated by ki-67 staining.

Flow cytometry

Three cases had flow cytometry information available for analysis, two from tissue specimens and one from a bone marrow specimen. In the two tissue cases the neoplastic cells were positive for CD19, CD20 and FMC-7; negative for CD5, CD10, and CD23. Both cases were kappa-restricted.

Although a small clonal B-cell population was detected by flow cytometric analysis of bone marrow aspirate in case 4, no evidence of lymphoma was detected in bone marrow biopsy by morphologic examination or immunohistochemistry, most consistent with monoclonal B-cell proliferation of undetermined significance.

Cytogenetics and molecular studies

We had cytogenetics or FISH data available for analysis in three of the four cases, which revealed no translocations that were characteristic for EMZL. In addition, there was no evidence of chromosomal rearrangement involving *IGH* locus in those cases. Polymerase chain reaction (PCR) analysis of *IgVH* gene rearrangement was carried out using paraffin-embedded tissue sections. In all cases a distinct band was identified, indicating the presence of clonal B-cells. We had sufficient material for Sanger sequencing of the PCR products in two cases (cases 2 and 4). Subsequent DNA sequence analysis using NCBI IgBLAST program revealed IgVH3-30 usage by B-cells in both cases.

Discussion

Most of the lymphomas occurring in uterus are due to secondary involvement by systemic lymphoma, with cervix being the most common site [4]. Primary lymphomas of the endometrium are rare; PEMZL-EM is extremely rare, with only nine cases having been previously

Table 2. A summary of the clinical and laboratory findings of the PEMZL-EM

Case no.	Age (years)	Clinical	Site	Histology	IHC	Clonality by PCR	Stage	F/U (Months)	Ref
1	81	Incidental finding; breast Ca	EM Polyp and stalk	Diffuse infiltration by small lymphocytes with narrow rim cytoplasm; GCs (+); LEL (+); BM (-)	CD20+CD79a+IRTA1+ CD10-cyclinD1 ND	N/A	IE	24	[7]
2	61	Incidental finding; Vaginal prolapse; hysterectomy	EM	Extensive nodular infiltrate; GCs (-); BM (N/A)	CD20+CD79a+CD5- CD10-CD23-BCL-6-, cyclinD1-	+	IE	8	[8]
3	52	Postmenopausal Bleeding; Enlarged uteus Fibroid; TAH-BSO	EM, BM	Prominent infiltrate; occasional LEL; BM (+) paratrabecular; leiomyoma	CD20+, CD5-, cyclinD1-	+	IVE	20	[9]
4	43	Intermenstrual bleeding Hypothyroidism; TAH-BSO	EM; Iliac lymph node	N/A BM (-)	N/A	N/A	IIE	28	[10]
5	65	Postmenopausal bleeding TAH-BSO	EM, sMM	Nodular, solid nest and sheets; occasional GCs, LEL (-); BM (-); EM polyp	CD20+CD5-CD10-BCL-6-cyclinD1-	+	IE	N/A	[11]
6	72	Pelvic pressure with dysuria Large uterine mass Granulomatous process in lungs; TAH-BSO	EM, MM pelvic lymph node	Monocytoid small lymphocytes admixed with large cells and plasma cells; LEL (+); GCs (+); BM (-)	N/ACD20+, CD5+, CD10-, CD23- (lymph node)	+	IIE	11[a]	[12]
7	80	Incidental finding; Uterovaginal prolapse; CIN3 and early invasive well-differentiated Ca; IgA kappa araprotein; Vaginal hysterectomy	EM, sMM Groin lymph node	Multiple nodules, superficial bands, perivascular and single cell infiltrate; plasma cells (clonal); GCs (-); LEL (-); BM (N/A)	CD20+CD5-CD10-BCL-6-IgD-	N/A	IIE	7	[6]
8	77	Incidental finding Hysterectomy for prolapse	EM, sMM	Nodular lymphoid infiltrate with a proportion of monocytoid cells; LEL (+); GCs (-); BM (N/A)	CD20+CD79a+CD43+ CD5-CD10-CD23- cyclinD1-	+	IAE	N/A	[5]
9	55	Vaginal bleeding EM polyp; TAH-BSO	EM and inner ½ of MM	Nodular lymphoid infiltrate; LEL (-); GCs (1); BM (-)	CD20+CD79+CD5+ CD10-CD23-cyclinD1-		IE	30	[13]
10	59	Vaginal bleeding Heptitis C	EM	Nodular and focal diffuse lymphoid infiltrate; GCs (-); LEL (-), BM (-)	CD20+CD5-CD10- cyclinD1-	+	IE	24	Pre
11	72	Vaginal bleeding	EM, sMM	Nodular lymphoid infiltrate; GCs (-); LEL (-); BM (-)	CD20CD79a+CD43+CD5-CD10-CD23-BCL-6-cyclinD1-	+	IE	60	Pre
12	58	Incidental findings Colonic cancer for staging	EM	Multiple lymphoid nodules; GCs (-); LEL (-); BM (N/A)	CD20+CD5-CD10-CD43+cyclinD1-	+	IE	24[b]	Pre
13	46	Vaginal bleeding	EM	Nodular lymphoid infiltrate; GCs (+); LEL (-); BM (N/A)	CD20+CD79a+CD5-CD10-cyclinD1-	+	IE	48	Pre

Abbreviations: a, radiotherapy; b, died of Ca; IHC, immunohistochemistry; F/U, follow up; Ref, reference; BM, bone marrow; Ca, carcinoma; CIN3, cervical intraepithelial neoplasia (grade 3); EM, endometrium; sMM, superficial myometrium; GCs, germinal centers; LEL, lymphoepithelial lesion; N/A, not available; TAH-BSO, Total Abdominal Hysterectomy Bilateral Salpingo Oophorectomy; Pre, present case.

described as single case report in English literature [5-13]. This is also reflected in our study that only four cases have been identified from the files of a large health care system during a period of 15 years. Our cases predominantly affected postmenopausal woman, with a median age of 59 years. Vaginal bleeding was the most common presentation and none of the patients had constitutional symptoms at the time of initial presentation. In majority of our cases the lymphoma was confined to the endometrium. Histological findings were similar in all cases, which was characterized by nodular lymphoid proliferation of small to medium-sized lymphocytes with either centrocyte-like or monocytoid morphology. Lymphoepithelial lesions, the pathognomonic feature of EMZL, were not seen in any of our cases. Plasmacytic differentiation was absent in all but one case. Residual germinal centers were rare. The nodular lymphoid proliferation pattern is quite characteristic for PEMZL-EM, which is uncommon for EMZL arising in other anatomic sites. All cases demonstrated the immunophenotype of marginal zone lymphoma, of which two expressed CD43. In all the cases, the diagnosis of lymphoma was supported by morphology, immunohistochemistry, and molecular analysis. Three of our patients were alive with no evidence of disease after a median follow-up of three years and one patient died of an unrelated malignancy. Although the follow-up period is relatively short, it appears that our patients had indolent clinical courses.

To further characterize this entity, we summarize the clinicopathological features of thirteen cases of PEMZL-EM including our cases in **Table 2**. The median age was 61 years (range, 43 to 81 years). The clinical presentation included the followings in descending order: abnormal vaginal bleeding (n=7), incidental finding (n=5), and pelvic pressure with dysuria (n=1). Other significant findings included cancer (n=3), endometrial polyps (n=3), leiomyomata (n=2), hepatitis C (n=1), hypothyroidism (n=1), and IgA paraprotein (n=1). In a majority of the cases (9/13) the lymphoma was limited to uterine corpus, only three cases had local lymph node involvement, and one case had bone marrow involvement. The histological findings were characteristic and the immunophenotype was that of marginal zone lymphoma in all but two cases. One case with CD5 positivity had regional lymph node involvement, for which he received radiation therapy. Only a subset of the reported cases had cytogenetics or FISH information available for analysis, which did not show the characteristic genetic alterations. The clinical course appeared to be indolent, with 10 out of 11 patients reported to be alive after a median follow-up of two years [5-13].

The etiology and pathogenesis of EMZL is still unclear and it has been speculated that antigen stimulation may play an important role. EMZL is often associated with chronic infections and autoimmune diseases. Examples of infectious organisms that may cause EMZL in mucosal or cutaneous sites include *Helicobacter pylori* (gastric mucosal-associated lymphoid tissue or MALT lymphoma), *Chlamydia psittaci* (ocular adnexal EMZLlymphoma), *Campylobacter jejuni* (immunoproliferative small intestinal disease), and *Borrelia burgdoferi* (cutaneous EMZL) [3]. However, there is no evidence of chronic endometritis in this cohort although human papillomavirus or hepatitis C virus was detected in two patients. Hepatitis C has been associated with nodal marginal zone lymphoma. In addition, no evidence of *Chlamydia psittaci* infection was observed in our cases, which has not been reported in other PEMZL-EM cases. Three characteristic chromosomal translocations have been described in EMZL of other sites: t(11;18)(q21;q21), t(1;14)(p22;q23) and t(14;18)(q21;q32) [15, 16]. The presence of these translocations is often associated with chronic infections and activation of NF-KB pathway [17]. Other genetic alterations such as trisomies also have been reported in EMZL arising in other sites [15, 16]. Although EMZL may carry one of these abnormalities, the incidence is variable depending on the anatomic sites and geographic locations. However, none of the translocations have been found in EMZL occurring at uncommon sites such as breast and prostate and, in our case, the endometrium [14, 15]. Furthermore, these translocations are also not detected in *C. psittaci* negative ocular adnexal extranodal marginal zone lymphoma (*C psittaci*-negative OAEMZL) [17]. These findings suggest that factors other than chronic infections may play an important role in the pathogenesis of these subtypes of EMZL and further studies are needed to identify the underlying molecular mechanisms.

In order to address this issue, we studied the usage of IgVH genes in our cases, which have not been previously explored. We acquired sufficient DNA for sequence analysis in two cases.

Surprisingly, in both cases the B-cells used IgVH3-30 family, which frequently encodes autoantibodies. Biased usage of IgVH3-30 has been reported at a higher frequency in *C psittaci*-negative OAEMZL and *H. pylori* eradication-responsive and *API2-MALT1* fusion-negative gastric EMZL [18, 19]. These findings suggest that chronic interaction with a biased immunoglobulin family subset with an unknown antigen may play a role in the pathogenesis of PEMZL-EM. However, the case number is too small to draw a definitive conclusion.

Our series of four patients with PEMZL-EM shows that this entity predominantly affects postmenopausal women and is characterized by distinct histologic features, characteristic immunophenotype, lack of specific genetic alterations, and indolent clinical course. We are the first to study the usage of IgVH gene in PEMZL-EM and found biased use of the IgVH3-30 family in two cases. Our findings suggest that chronic antigen stimulation may play an important role in the pathogenesis of PEMZL-EM.

Disclosure of conflict of interest

None.

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