

Extranodal marginal zone lymphoma of the uterine cervix with concomitant copy number gains of the *MALT1* and *BCL2* genes: A case report

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Abstract. Extranodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) of the uterus is rare, and the etiology, pathophysiology and cytogenetic features remain unknown at present. The present study reports a case of a 71-year-old female with EMZL of the uterine cervix that was 80 mm in diameter and invaded directly into the rectal serosa. Complete remission was successfully induced by 6 courses of immunochemotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone. Although the metaphase spread of the tumor cells was unavailable for whole cytogenetic analysis, fluorescence *in situ* hybridization (FISH) detected triple signals for *MALT1* and B-cell lymphoma 2, located at chromosome 18q21, and the centromere of chromosome 18, which was suggestive of trisomy 18, and in combination with previous studies, suggested a possible association between trisomy 18 and the large tumor at initial presentation in the present patient. In addition, FISH examination detected immunoglobulin heavy chain gene rearrangement, although the translocation partner was unconfirmed. A total of 18 previously-studied patients with EMZL of the uterus, including that of the present study, were reviewed with respect to their clinical features and treatment and cytogenetic abnormality. In the evaluation of the English scientific literature, this is the first reported patient with EMZL of the uterus with partly determined cytogenetic abnormalities.

Introduction

Extranodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) is a subtype of indolent non-Hodgkin lymphoma that develops in the extranodal organs, such as the stomach, salivary glands, ocular adnexa and the thyroid (1). Repeated cytogenetic alterations include reciprocal chromosomal translocations such as t(11;18)(q21;q21) in *Helicobacter pylori* infection-unassociated gastric EMZL (2), t(14;18)(q32;q21) in ocular adnexa EMZL, t(1;4)(p22;q32) in intestinal and pulmonary EMZL and numerical abnormalities such as trisomy of chromosome 3 or chromosome 18 (3,4). These alterations are valuable as diagnostic markers and for understanding the molecular pathophysiology of the lymphomagenesis of EMZL (5). The aforementioned chromosomal translocations are usually mutually exclusive, and their frequencies vary widely depending on the primary tumor site. Furthermore, these chromosomal translocations and numerical abnormalities frequently co-exist in tumor cells from individual patients.

Primary lymphoid neoplasms of the uterus are rare, accounting for ~2.0% of extranodal lymphomas and for <0.5% of gynecologic cancer (6). In addition, the majority of primary uterus lymphomas are high-grade subtypes, such as diffuse large B-cell lymphoma (DLBCL) (7), whilst the occurrence of EMZL of the uterus is rare, with only 17 previously reported cases in the English literature (8-21), and their cytogenetic/genetic characteristics remain unknown. The present study reports a patient with primary uterine cervical EMZL with the concomitant copy number gains of *MALT1* and B-cell lymphoma 2 (*BCL2*) genes, which are located at chromosome 18q21. As the tumor cells also harbored triple centromeres of chromosome 18, the lymphoma cells in the patient of the present study were suggestive of trisomy 18. In addition, the clinical features of previously reported cases of EMZL of the uterus were reviewed. In this examination of the English literature, the present study is the first case of uterine cervical EMZL in which cytogenetic abnormalities were at least partly determined.

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Case report

Patient. A 71-year-old female was referred to University Hospital of Kyoto Prefectural University of Medicine (Kyoto, Japan), complaining of abnormal vaginal bleeding. She exhibited no B symptoms, such as pyrexia, night sweating or body weight loss at presentation. Vaginal examination identified abnormal thickening of the vaginal wall (Fig. 1A), and transvaginal ultrasound sonography detected a large mass, 80 mm in diameter, at the uterine cervix (Fig. 1B). T2-weighted magnetic resonance imaging detected a slightly high-intensity tumor at the uterus cervix that invaded directly to the rectal serosa (Fig. 1C and D). Positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose (FDG) integrated with computed tomography also detected the presence of enlarged FDG-avid lymph nodes in the pelvis, whilst other lesions were intact (Fig. 2). The serum soluble interleukin-2 receptor level was elevated to 1230 U/ml, normal range; 122-496 U/ml, whilst other laboratory tests were normal, including blood cell counts, lactate dehydrogenase, C-reactive protein and albumin. The serum antibody test for *Chlamydia trachomatis* was negative. Histological examination of the biopsied specimen of the tumor revealed infiltration of small and round-shaped abnormal lymphoid cells with oval or convoluted nuclei that were positive for cluster of differentiation (CD)20, CD79a and BCL2 markers (Fig. 3A-D), but were negative for CD5, CD10, cyclin D1, BCL6, or pan-cytokeratin markers (data not shown). These results were consistent with the results obtained by flow cytometric analysis, which detected the presence of CD19-phycoerythrin (PE)-cyanin 5.1 (Beckman Coulter, Inc., Brea, CA, USA) and CD20-fluorescein isothiocyanate (FITC), but the absence of CD5-FITC or CD10-PE (BD Biosciences, San Jose, CA, USA). Additionally, flow cytometry also revealed the expression of surface immunoglobulin (Ig) λ chain of tumor cells (data not shown). Collectively, the patient was diagnosed with EMZL, stage II according to the Ann Arbor staging system (22). The patient was treated with 6 courses of rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP): Rituximab 375 mg/m² on day 1, cyclophosphamide 750 mg/m² on day 2, doxorubicin 50 mg/m² on day 2, vincristine 1.4 mg/m² on day 2, prednisolone 100 mg/body on days 2-6, and attained complete response (CR). She has maintained CR for 9 months at the time of writing. Informed consent was obtained from the patient.

Procedure and result by the interphase fluorescence in situ hybridization (FISH) analysis. Single- and double-color FISH in single cell preparations of patient-derived lymphoma cells were performed as previously described (23). In addition, FISH was performed on paraffin-embedded tissue sections, tissue-FISH, according to previously described methods (24). The LSI Dual Color sets for the IGH Break Apart Rearrangement Probe (Abbott Molecular Inc., catalog no. 8L63-20), a mixture of 2 probes that hybridize to opposite sides of the joining gene segment through constant regions of the Immunoglobulin heavy chain (IgH) locus, were used to detect chromosomal breakage at the *IgH* gene. The LSI Dual Color set for the MALT1 Break Apart Rearrangement Probe was utilized to detect the gene rearrangement of *MALT1*. The

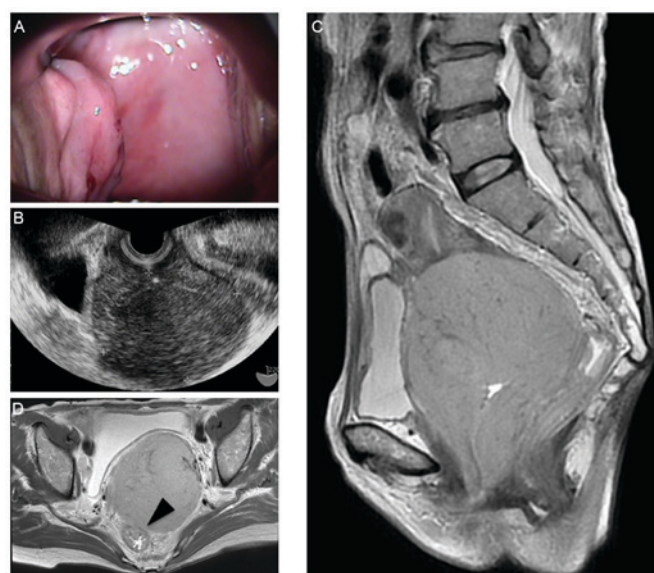


Figure 1. Gross appearance of uterine cervical tumor. (A) Vaginal examination identified the abnormally thickened vaginal wall and (B) transvaginal ultrasound sonography detected a large mass, 80 mm in diameter, adjacent to the cervix. (C) Transverse and (D) sagittal T2-weighted magnetic resonance imaging detected a slightly high-intensity tumor at the uterine cervix that directly invaded the rectal serosa (triangle).

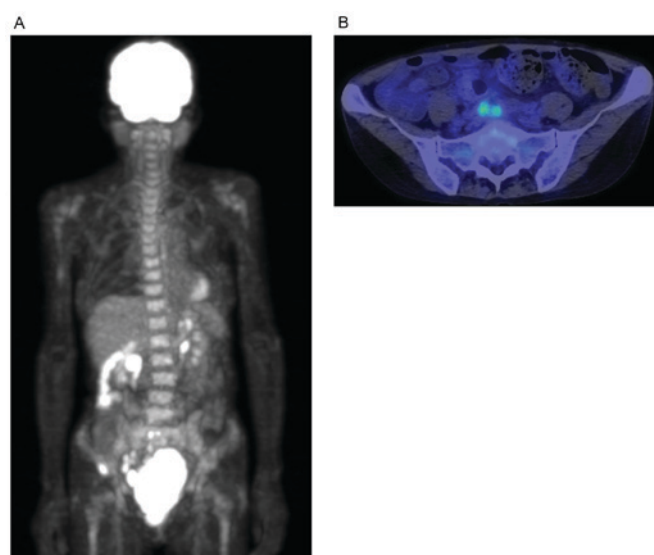


Figure 2. PET findings of ¹⁸F-FDG PET/CT. ¹⁸F-FDG PET/CT revealed the presence of (A) a FDG-avid large tumor (coronary image of the whole body) and (B) enlarged lymph nodes in the pelvis (transverse image of the pelvis). PET, positron emission tomography; ¹⁸F-FDG PET/CT, 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with computed tomography.

LSI Dual Color sets for the fusion genes of *MALT1/API2*, *MALT1/IgH*, *BCL2/IgH*, or *MYC/IgH* (Abbott Molecular Inc., Des Plaines, Ill., USA) were also utilized in the present study. Vysis Chromosomes Enumeration Probe 18 (CEP18) (catalog no. 05J08-028; Abbott Molecular Inc.) was used to detect the centromeric region of chromosome 18.

As the metaphase spreads were unavailable due to the lack of dividing cells in the biopsied specimens, the cytogenetic studies were performed using interphase FISH. Although the FISH probes that specified chromosomal translocations

Table I. List of cases of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue of the uterus.

		Clinical presentation	Site	Gross appearance				Treatment	FISH				(Refs.)
				Normal	Polyp	Tumor	Stage		t(11;18)	t(14;18)	t(1;14)	Other	
1	80	Vaginal prolapse	Corpus	+	-	-	II	Hysterectomy	Neg.	Neg.	Neg.	-	(7)
2	58	Incidental	Corpus	+	-	-	I	Hysterectomy	Neg.	Neg.	-	-	(8)
3	46	Bleeding	Corpus	+	-	-	I	Hysterectomy	Neg.	Neg.	-	-	(8)
4	59	Bleeding	Corpus	+	-	-	I	Hysterectomy	Neg.	Neg.	-	-	(8)
5	72	Bleeding	Corpus	+	-	-	I	None	Neg.	Neg.	-	-	(8)
6	61	Incidental	Corpus	+	-	-	I	Hysterectomy	-	Neg.	-	-	(9)
7	43	Bleeding	Corpus	+	-	-	II	TAH-BSO+LN sampling	-	-	-	-	(10)
8	47	Dysmenorrhea	Corpus	+	-	-	I	TAH-BSO	-	-	-	-	(11)
9	52	Bleeding	Corpus	+	-	-	IV	TAH-BSO	-	-	-	-	(12)
10	77	Incidental	Corpus	+	-	-	I	Hysterectomy	-	-	-	-	(13)
11	81	Incidental	Corpus	-	+	-	I	-	-	-	-	-	(14)
12	55	Bleeding	Corpus	-	+	-	I	TAH-BSO	-	-	-	-	(15)
13	65	Bleeding	Corpus	-	+	-	I	TAH-BSO	-	-	-	-	(16)
14	72	Dysurea	Corpus	-	-	+	II	TAH+RT	-	-	-	-	(17)
15	46	Bleeding	Cervix	-	+	-	IV	ProMACE/CytaBOM hysterectomy	-	-	-	-	(18)
16	56	Vaginal spotting	Cervix	-	-	+	I	Hysterectomy with bilateral salpingo-oophorectomy+RT+Rit	-	-	-	-	(19)
17	53	Cervical dysplasia	Cervix	+	-	-	I	Conization	-	-	-	-	(20)
18	71	Bleeding	Cervix, Vagina	-	-	+	II	R-CHOP	Neg.	Neg.	Neg.	Trisomy 18	Present study

FISH, fluorescence *in situ* hybridization; BSO, bilateral salpingo-oophorectomy; TAH, total abdominal hysterectomy; LN, lymph node; proMACE/cytaBOM, cyclophosphamide, epirubicin, etoposide, prednisone, cytarabine, vincristine, bleomycin and methotrexate; RT, radiation therapy; Rit; rituximab; Neg., negative; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

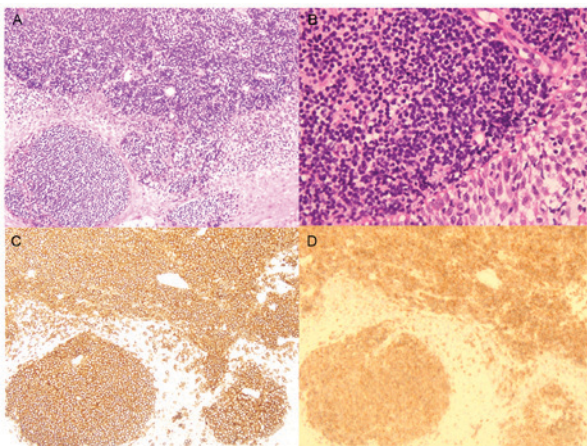


Figure 3. Histological findings. Hematoxylin & eosin staining of a biopsied specimen from the uterine cervical tumor revealed infiltration of small and round-shaped abnormal lymphoid cells with oval or convoluted nuclei in the uterine cervix, leading to the diagnosis of extranodal marginal zone lymphoma at (A) magnification, x100 and (B) magnification, x400 (light microscope). Immunohistochemical staining using the Ventana iVIEW DAB Universal Kit (Ventana Medical Systems, Inc., Oro Valley, AZ, USA) revealed that the abnormal lymphoid cells expressed (C) cluster of differentiation 20 stained with anti-CD20 antibody (L26) (Roche Diagnostics, Branchburg, NJ, USA) at magnification, x100 and (D) B-cell lymphoma 2 stained with anti-BCL2 antibody (clone 124) (Dako; Agilent Technologies, Inc., Santa Clara, CA, USA) at magnification, x100.

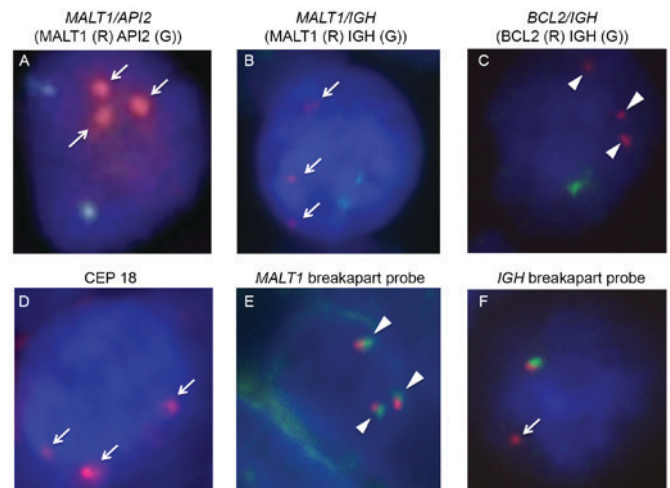


Figure 4. FISH analyses. (A-C) Whilst double-color FISH analyses for the *API2/MALT1*, *IgH/MALT1*, and *IgH/BCL2* fusion genes were negative, these examinations revealed that the tumor cells harbored triple copies of (A, B) *MALT1* (arrows) and (C) *BCL2* (arrowheads). The tumor cells harbored (D) three centromeres of chromosome 18 (arrow), whilst (E) the *MALT1* gene was not rearranged (arrowheads). (F) FISH evaluation also identified the *IgH* split signal, indicating the presence of *IgH* gene rearrangement (arrow). FISH, fluorescence *in situ* hybridization; CEP, chromosome enumeration probe; *MALT1*, mucosa associated lymphoid tissue lymphoma translocation gene 1; *IgH*, immunoglobulin heavy locus; *BCL2*, B-cell lymphoma 2.

at t(11;18)(q21;q21) for the *MALT1/API2* fusion gene, t(14;18)(q32;q21) for the *MALT1/IgH* fusion gene and t(14;18)(q32;q21) for the *BCL2/IgH* fusion genes did not demonstrate the presence of the respective fusion genes, these examinations identified that the tumor cells harbored triple copies of the *MALT1* and *BCL2* genes (Fig. 4A-C). In addition, the tumor cells also harbored three signals for chromosome enumeration probe 18, indicating the existence of centromeres of chromosome 18 (Fig. 4D), and three copies of the non-rearranged *MALT1* gene (Fig. 4E). Collectively, these results suggested the existence of trisomy 18 in the tumor cells. Whilst the FISH examination also identified the *IgH* split signal, which indicated the presence of *IgH* translocation, the translocation partner, including *c-MYC* (*MYC*), was not identified (Fig. 4F and data not shown).

Discussion

Fox and More (25) defined the criteria for the diagnosis of primary extranodal lymphoma of the uterus as follows: Clinically confined to the uterus, no evidence of leukemia and along interval between the appearance of primary uterine lymphoma and the secondary tumor. The patient of the present study fulfilled these criteria. Amongst the previously reported cases of uterine EMZLs, including the patient of the present study (Table I), the development of EMZLs in the uterine cervix were even more rare, with only 4 reported patients (19-21). With respect to the gross appearance of the tumors of 18 cases, 15 were small in size, located in grossly normal epithelium or in small polyps, and were incidentally identified by the screening biopsy (Cases 1-13, 15 and 17 in Table I). Large tumors, as in the patient of the present study, were extremely rare. Cytogenetic analyses using FISH were administered to 6 previously reported cases, yet they failed to detect any particular chromosomal abnormalities (Cases 1-6 in Table I) (8,9). In the patient of the present study, trisomy 18 and *IgH* translocation were suspected, although not determined definitively due to the lack of sufficient material for metaphase spreads. Thus, the present study is the first study to identify partial chromosomal abnormalities in EMZL of the uterus.

Trisomy 18 has been associated with the levels of clinical aggression in gastric EMZL (26). In addition, Sugimoto *et al* (27) reported a case of DLBCL of the uterus harboring trisomy 18 that was suspected to have been transformed from EMZL. These suggest a potential association between trisomy 18 and the large tumor at initial presentation in the present study. Conversely, whilst rearrangement of the *IgH* gene in the lymphoma cells was identified in the present patient, the translocation partner was not. Furthermore, investigation of the t(8;14)(q24;q32) for the *IgH/MYC* fusion gene was negative (data not shown). In addition, as the immunohistochemical analysis revealed that BCL6 was negative in the tumor specimen, the t(3;14)(q27;q32) alteration was unlikely to exist. Thus, the pathogenic involvement of the *IgH* translocation remains unknown in the present study.

Whilst localized therapies, including surgical resection and radiotherapy, have been generally adapted to EMZL in the limited disease stage, systemic immunochemotherapy R-CHOP as the initial treatment was administered to the patient in the present study for several reasons. Firstly, the large

tumor invaded directly to the rectal serosa at presentation, and radiotherapy was considered high risk for rectal penetration or rupture. It was also anticipated that the wide field irradiation for the large tumor may lead to unwanted adverse events in the pelvic viscera. Secondly, surgical resection was also excluded, as complete resection of the large tumor and the additionally involved lymph nodes required pelvic evisceration. To avoid those invasive therapy-associated complications, systemic immunochemotherapy was selected. However, EMZL is generally a clinically indolent disease with a 5-year overall survival ranging from 86 to 100% (28,29). The optimal approach for the management of uterine EMZL has not yet been established, and the treatment choice should be carried in consideration of the tumor site, disease stage and clinical manifestations on an individual basis. In conclusion, the present study reports the first case of uterine cervical EMZL with trisomy 18 and *IgH* translocation with an unknown partner, as detected by FISH analyses.

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