Original Article
Primary lymphoma of the female genital system: a report of four cases

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Abstract: Female patients with primary lymphoma of the female genital system (PLFGT) are extremely rare, accounting for only 1-3% of all cases of extra-nodal lymphoma. Given its rarity, there is still no standard consensus regarding the optimal management strategy for this disease. The current study presents four cases of PLFGT. All patients were postmenopausal women admitted to the hospital for pelvic mass or postmenopausal vaginal bleeding, with two of them harboring c-myc and bcl-2/bcl-6 co-expression, termed as "double-expressor" (DE) lymphomas. To the best of our best knowledge, this is the second article describing DE diffuse large B-cell lymphoma (DLBCL) confined to the female genital tract. One of the patients developed an early relapse in the central nervous system within three months. The aim of this study was to spread awareness among clinicians about the rarity of this disease and, especially, the aggressive nature of this neoplasm. Therefore, reporting these new cases may help in understanding clinical characteristics and prognosis of this disease. In a clinical setting, for elderly postmenopausal women complaining abdominal mass, clinicians and pathologists should suspect the possibility of PLFGT, making a more timely and accurate diagnosis.

Keywords: Cancer antigen-125, double-expressor lymphoma, female genital system, immunohistochemistry, primary lymphoma

Introduction

Lymphoma is a common hematological malignancy subcategorized into Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL) [1]. NHL accounts for 70-80% of all lymphomas. It accounts for 3.5% of all malignant neoplasms in females. Approximately, up to 40% of lymphomas derive from extra nodal tissues. It is more commonly seen in the gastrointestinal tract and skin [2, 3], but it can occasionally arise from other sites, such as breasts, thyroid, adrenal glands, and female genital tract [4-7]. Hematological malignancies, involving the female genital tract, are mostly lymphomas. Involvement of secondary, rather than primary lymphoma, is more commonly seen. The ovary is the organ that is mostly affected. Patients with primary lymphomas of the female genital system (PLFGT) are extremely rare, accounting

for only 1-3% of all cases of extra-nodal lymphoma [3, 8, 9]. Incidence of involvement of the genital tract secondary to disseminated lymphoma is up to 40% [8-10]. NHL constitutes most of the cases of the female reproductive system, with diffuse large B-cell lymphoma (DLBCL) the predominant histologic subtype [11-13]. U. Salem et al. demonstrated that whenever a large homogeneous mass is seen involving the female genital tract, it is worthy of attention [14]. Their definite diagnosis relied on biopsies. Given the rarity of PLFGT, there is still no consensus regarding the optimal management strategy. Treatment regimens include surgery, chemotherapy, radiotherapy, or a combination of these modalities. In recent decades, there have been dramatic advances in diagnosis and treatment of lymphoma. However, primary lymphomas of the female genital system remain a great threat to the health of women. The pres-

ent study reported four cases of PLFGT. Patients were postmenopausal women admitted to hospital with a complaint of pelvic mass or postmenopausal vaginal bleeding, with two of them harboring c-myc and bcl-2/bcl-6 co-expression, called "double-expressor" (DE) lymphomas.

Case presentation

Case 1

A 69-year-old postmenopausal woman was admitted to the hospital with the presence of a right lower abdominal mass for four days. Upon gynecologic examination, a solid pelvic mass of 11×7 cm was palpated. No other abnormalities were noted. Ultrasonography examination revealed a bilateral inguinal lymphadenopathy. No tumor cells were found via multiple lymph node biopsy and serum tumor indicators were within the normal range. Serum lactate dehydrogenase (LDH) was elevated to 331 U/L. Computed tomography (CT) of the abdomen demonstrated diffuse thickening of the peritoneum and tumor metastasis was considered. She received an exploratory laparotomy and right partial oviductomy. During the operation, an irregular mass of 13×5×7 cm was seen above the right iliac vessel. Pathological analysis showed NHL. Immunohistochemistry analysis of the resected specimen revealed bcl-6, c-myc, EBER, CD20, Mum-1, and P53 positive, displaying a high proliferative index with 99% staining of Ki-67. Bcl-2, CD10, and p63 were negative, while Epstein-Barr virus (EBV) (+) DLBCL activated B-cell type. Post-operative systematic evaluations included chest radiography, and computed tomography of the thorax. Routine peripheral blood findings and bone marrow examinations did not show any evidence of extragenital primary disease. After these evaluations, the patient was treated with three cycles of R-EPOCH (rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. After the third cycle of chemotherapy, the patient began to complain about dizziness and blurred vision. Brain CT scans revealed a high-density nodule, suspected to be lymphoma of the brain. The patient refused further treatment and died within 3 months after the relapse.

Case 2

A 62-year-old postmenopausal woman presented to her gynecologist, complaining of backache and a pelvic mass for three days. She denied any other symptoms. Gynecologic examinations revealed a solid pelvic mass of 8×9 cm in her right adnexa. There was no palpable lymph node or hepatosplenomegaly during physical examination. Transvaginal ultrasonography confirmed a bulky inhomogeneous mass, sized approximately 97×76×85 mm in diameter, in front of the uterus. CT scans of the abdomen showed a possibility of malignancy in pelvic and peritoneum. Her serum cancer antigen 125 (CA-125) level was elevated to 221.5 U/mL and her LDH level was 566 U/L. The patient underwent "hysterectomy with bilateral salpingectomy". Pathological analysis demonstrated right adnexal lymphoma. Immunohistochemistry analysis showed that tumor cells were positive for CD20, Mum-1, and CD79α and were negative for bcl-2, bcl-6, EBER, CD10, and CD21. Ki-67 immunostaining showed an elevated proliferative index of 60%. The patient was ultimately diagnosed with DLBCL, non-germinal center B (GCB) cell-type. She received six-cycles of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicine, vincristine, and prednisone) chemotherapy, which was well-tolerated. After finishing all six courses, she used rituximab as maintenance monotherapy. After five months of follow-ups, the patient was admitted to the Hematology Department with a palpable abdominal mass. The patient had an ultrasound abdominal biopsy. Pathological results demonstrated a relapse. She then accepted three cycles of RR-MINE (rituximab, mitoxantrone, etoposide, Ifosfamide, mesna) regimen and abdominal CT scans showed a decrease in tumor size. One month after finishing the last chemotherapy, the patient complained about thoracalgia and was referred to our department again. B-ultrasound examination revealed pleural effusion. Pathological analysis of the fluid demonstrated flaky heterotypic lymphoid cells. She was diagnosed as lymphoma with pleural infiltration. A chemotherapy regimen of Lenalidomide plus EPOCH (etoposide, cyclophosphamide, daunorubicine, vincristine, and prednisone) was used. The patient had an overall survival (OS) of 19 months.

Case 3

A 45-years-old postmenopausal woman was admitted to the hospital for a pelvic mass found

during a routine physical examination eight months earlier. She complained of weakness and emaciation for a month, without fever, night sweats, and vaginal bleeding. The patient had a history of subtotal hysterectomy because of uterine leiomyoma. Gynecologic examinations revealed a huge pelvic mass, which was up to the umbilical level, with both sides reaching the midline of the clavicle line. Pelvic ultrasound confirmed two hypoechoic solid masses, sized 125×82×104 mm and 97×89×88 mm, respectively. Her CA-125 level was elevated to 251.3 U/mL. The level of the LDH was elevated to 410 U/L. She received ovarian cytoreductive surgery. Intraoperative findings revealed no uterus with ovaries that had bilateral masses, with the left measuring approximately 12×8×10 cm and the right 10×9×9 cm. Pathological analysis revealed bilateral adnexal lymphoma. The patient had no major lymphadenopathy. Immunohistochemistry analysis demonstrated that most of the lymphocytes stained positively for bcl-2, bcl-6, c-myc, and CD20 and showed a proliferative index with a 60% staining with Ki-67. The patient was finally diagnosed as DLBCL. Post-operative radiographic imaging of the chest and abdomen was normal. After the operation, the patient received R-CHOP chemotherapy, followed by seven cycles of CHOP regimen, which was well-tolerated. One year later, the patient felt a thickening of the abdominal wall. A routine B-ultrasonography revealed an abdominal wall mass. Aspiration biopsy confirmed tumor invasion. Therefore, the patient accepted a course of R-CHOP chemotherapy, after which the mass shrank rapidly. Subsequently, she received another six cycles of R-CHOP chemotherapy regimen as consolidation therapy. One year after the end of chemotherapy, the patient received several regimens of radiotherapy. During this period, she gradually developed thrombocytopenia, carcinomatous pain, and cardiac insufficiency. The patient had an OS of 32 months.

Case 4

A 77-years-old postmenopausal woman complaining of vaginal bleeding for a month was referred the Gynecology Department. A cytological smear of the cervix showed no intraepithelial lesions or malignant lesions. Fractional curettage revealed small cell malignancy of endometrium. Tumor markers were within the normal range. Pelvic Magnetic Resonance Imaging (MRI) revealed endometrial carcinoma, which had invaded the outer myometrium of the uterus. There was no obvious lymphadenopathy in the pelvic cavity. The patient received a laparoscopic hysterectomy with bilateral salpingo oophorectomy, laparoscopic radical resection of pelvic lymph nodes, and electrocision of vaginal lesions. Surgical exploration showed a 1×1 cm polypoid neoplasm at the anterior fornix of the vagina. Immunohistochemistry of surgical specimens was positive for c-myc, bcl-6, PAX5, MUM-1, and CD20 and negative for bcl-2, p53, and p63. The patient was finally diagnosed as DLBCL, non-GCB type. Pathological results were negative for lymph node invasion. A post-operative complete clinical work-up, including chest radiograph, B-ultrasonography of abdomen, and peripheral blood examination, did not demonstrate any extragenital primary disease. After the operation, the patient did not receive either radiotherapy or chemotherapy. After twelve months of follow-up, the patient remains alive.

Discussion

PLFGT is an extremely rare disease, accounting for about 1-3% of extranodal lymphoma [3, 8, 9]. It is derived from B-cells, with DLBCL the predominant histologic subtype [11-13].

Currently, the most common sites of occurrence in the genital tract are controversial. A SEER database study identified 697 cases reported from 1988 to 2012. The ovary was the most common primary site (36%), followed by the cervix (21.4%), uterus (16.5%), vagina (11.8%), vulva (8.2%), other (5.2%) [15]. Clinical presentation of PLFGT tends to be non-specific, including pelvic masses, abnormal vaginal bleeding, increased vaginal discharge, abdominal fullness, and abdominal pain. Some patients are even completely asymptomatic with an incidental finding of a pelvic mass (Case 1). Moreover, most patients lack classic B symptoms of lymphoma. In addition, to our best knowledge, there are no definite imaging findings for diagnosis for PLFGT thus far. Differentiation between primary and secondary lymphoma remains challenging. Accurate clinical diagnosis of PLFGT can be difficult. It can be easily confused with other gynecological malignancies [8], such as endometrial cancer, cervical cancer, sarco-

Table 1. Clinical characteristics of the four reported patients with primary lymphoma of the female genital system

Case	Age	IPI	CA-125 (U/ml)	LDH (U/L)	Primary site	Stage (FIGO)	Pathological type	IHC		Treatment condition	OS (m)	CNS relapse	Survival status
								Bcl-2/bcl-6	cmyc				
1	69	3	12.9	331	Fallopian tube	IV	DLBCL (EBV+)	-/3+	30%+	Operation Chemo-	3	Yes	died
2	62	2	221.5	566	Adnexa	II	DLBCL (non-GCB)	-/-	NA	Operation Chemo-	19	No	died
3	45	3	251.3	410	Ovary	IV	DLBCL (non-GCB)	4+/+	30%+	Operation Chemo- Radio-	32	No	died
4	77	1	23.6	234	Endometria	I	DLBCL (non-GCB)	-/3+	10%+	Operation	12	No	alive

Abbreviations: CA-125: cancer antigen-125; FIGO: International Federation of Gynecology and Obstetrics; IPI: International prognostic index; LDH: Lactate dehydrogenase; EBV: Epstein-Barr virus; IHC: Immunohistochemistry; OS: overall survival; m: month(s); CNS: central Nervous System; DLBCL: diffuse large B-cell lymphoma; GCB: germinal center B; chemo-: chemotherapy; radio-: radiotherapy; NA: not acquired.

ma, or ovarian cancer, depending on disease site. PLFGT usually originates from and remains localized to the female reproductive organ system without any evidence of leukemia at the time of diagnosis. To make a definite diagnosis, histopathology and immunohistochemistry examinations must be carried out. Patients with PLFGT vary in age, with a median age of 44-62 years old [16-19]. In conclusion, for elderly women complaining with pelvic masses in clinical practice, a diagnosis of lymphoma should not be ignored. Early and accurate diagnosis significantly affects clinical outcomes [20]. In recent years, literature concerning PLFGT has mainly consisted of case reports or cases series. Therefore, very little is known about therapeutics options and prognosis. The most widely accepted treatment strategy is surgery, along with chemotherapy, with or without radiotherapy, and immunotherapy.

The four cases, in the present study, were all postmenopausal woman. Three of these were admitted to the hospital with the presence of a pelvic mass. One patient was referred to the clinician with abnormal vaginal bleeding as her complaint. General characteristics of the four cases are outlined in **Table 1**. Radiological examinations suspected malignancies, after which all four patients received gynecologic surgery. Final histology of the four surgical samples showed diffuse lymphoid cells proliferating and infiltrating (**Figure 1**). Currently, there are no definite immunohistochemical markers that exist to diagnose PLFGT. Undoubtedly, immunohistochemistry plays a pivotal role in the diagnosis and differential diagnosis of PLFGT. In this case series, immunohistochemistry profiles of all showed positivity for CD20

and negativity for CD10, cyclin-D1, and CD3. Postoperative histopathology, combined with immunohistochemistry, confirmed the diagnosis of DLBCL in all four cases. Once diagnosis of NHL has been confirmed, a complete staging workup must be settled [21], including full body CT and/or positron emission tomography (PET) scans followed by a bone marrow examination. These help distinguish between primary and secondary lymphoma. Systemic examinations of all four patients, including chest radiograph and computed tomography of the thorax, did not show any evidence of extragenital primary disease. No abnormal cells were found in bone marrow examinations (Case 1, Case 2, and Case 3). However, Case 4 did not take a bone marrow puncture and no juvenile cells were detected in peripheral blood. This preliminary eliminated a diagnosis of leukemia. Ultrasonography examinations demonstrated bilateral inguinal lymphadenopathy in Case 1. However, multiple lymph node biopsies were performed, with results showing no evidence of tumor cells. In conclusion, drawing on widely accepted diagnostic criteria (**Table 2**), each of the mentioned patients received a diagnosis of primary female genital tract diffuse large B-cell lymphoma.

According to the revised World Health Organization (WHO) classification of lymphoid neoplasms, published in 2016, co-expression of two proteins (MYC and BCL2 and/or BCL6) on more than a specified proportion of tumor cells based on immunohistochemistry staining is termed a DE lymphoma [22]. This constitutes a specific group with highly aggressive clinical behavior and extremely poor outcomes. Among two of the four patients, thirty-percent of malignant cells were positive for c-MYC immunoreac-
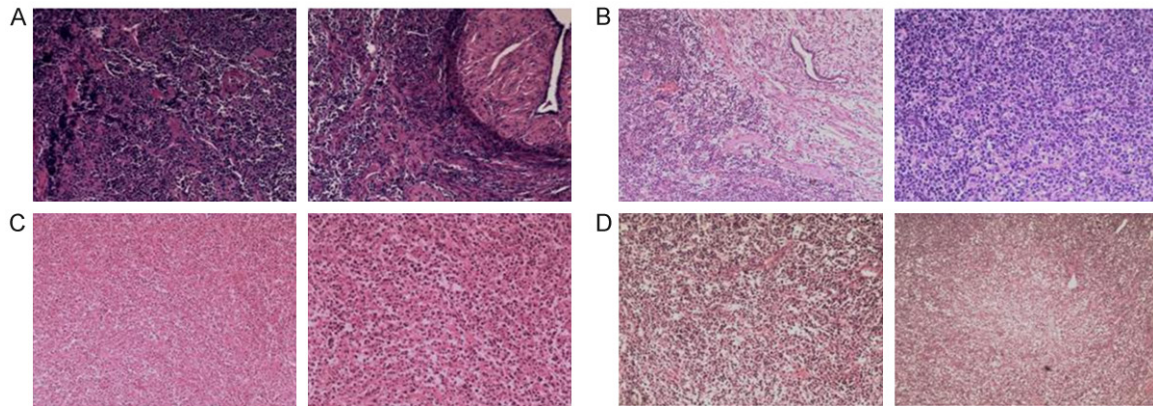
Figure 1. Histologic features of tumors. A. The sample showing lymphoid cells proliferating, infiltrating, and damaging the fallopian tube wall. B. Diffuse lymphoid cells infiltration of oviduct mucosa and right attachment. C. Lymphoid cells with consistent morphology proliferating and infiltrating the sample. D. Diffuse lymphoid cells infiltration of endometria.

Table 2. Diagnostic criteria of PLFGT

Diagnostic criteria
1. The disease process is clinically confined to a reproductive system organ
2. Full investigation fails to show any evidence of extragenital primary disease
3. Bone marrow examination or the blood count shows no evidence of leukemia
4. A long interval between primary lymphoma and the secondary tumor

Abbreviations: PLFGT: Patients with primary lymphoma of the female genital system.

tion (Case 1, Case 3), making them DE DLBCL confined to the female reproductive tract, with overexpression of c-MYC and bcl-2/bcl-6. To the best of our knowledge, this is the second article to describe DE DLBCL of the female genital tract (Case 1, Case 3). Alexandra et al. described a 69-year-old woman with the presence of a complex ovarian mass, according to CT scans. She underwent total robotic hysterectomy, bilateral salpingo-oophorectomy, and was diagnosed as stage IE (Ann Arbor) primary non-germinal center, DE DLBCL in a uterine leiomyoma. After surgery, the patient received three cycles of R-CHOP chemotherapy. At the end of the follow-up, she was still undergoing treatment and tolerating it well [23]. In this article, Case 1 received three cycles of R-EPOCH chemotherapy. Case 3 received chemotherapy combined with radiotherapy after the operation. Xin-xin et al. proposed that patients with primary DLBCL of the female genital tract have a high risk of central nervous system relapse and short progress free survival (PFS) [24]. In the present article, one of the two DE PLFGT developed early relapse in the central nervous system with a short OS of 3 months. Given the aggressive nature of this neoplasm, central nervous system prophylaxis might be considered in addition to systemic chemotherapy in PLFGT. However, the results above were not statistically significant, in part, because of its rarity. This issue requires further validation.

Simultaneously, among the four cases, two patients (Case 2, Case 3) showed elevated CA125 levels. However, elevated serum tumor indexes are not specific to lymphoma. Allen et al. pointed out that the increase of CA125 levels was associated with a decline of 5 year survival rates of patients with primary reproductive system lymphoma [25]. Shilpa et al. reported five cases of PLFGT, two of these with elevated CA125 levels got early onset of central nervous system involvement [26]. Regarding patients supported in this report, the OS of Case 2 was 19 months, while the OS of Case 3 was 32 months. It is noteworthy that the four PLFGT were all postmenopausal woman, three of whom were over 60 years old. This suggests that mechanisms of the disease may be related to menstrual cycle and estrogen levels.

Prognosis of PLFGT patients differs in different studies. Overall survival is associated with age, stage, histopathological type, and comorbidity. LDH can be used as prognostic indicator of this

Table 3. FIGO staging systems

FIGO Staging Systems
Stage I, tumor restricted to the lining and deeper tissue of involved organ (including bilateral ovarian involvement)
Stage II, spread by contiguity to immediately contiguous tissues
Stage III, involvement of regional lymph nodes
Stage IV, presence of distant metastasis

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics.

disease. In the present article, LDH levels of Case 1, 2, and 3 were elevated. Regarding staging workup, there still exists certain controversy about International Federation of Gynecology and Obstetrics (FIGO) and Ann Arbor staging standards. Since PLFGT is a gynecologic malignancy, FIGO staging criterion was adopted (**Table 3**) [9]. At present, International prognostic index (IPI) has proven to be a useful prognostic indicator for lymphoma, evaluating prognosis relying on clinical characteristics. It is widely used for risk stratification of patients. With the continuous emergence of new molecular prognostic indicators, prognosis of the clinical evaluation system has been gradually weakened. New molecular prognostic indicators, including c-myc, Bcl-2, p53, and so forth have emerged [27, 28].

TP53 plays a pivotal role in the regulation of cell cycle and proliferation. TP53 mutation can lead to gene instability, which induces non-controlled proliferation of tumor cells. Numerous studies have confirmed that mutation or deletion of the TP53 gene is an independent prognostic factor of lymphoma [29, 30]. The MYC gene, located on chromosome 8, encodes MYC proteins, which is a transcription factor that plays an important role in the regulation of cell growth, differentiation, and malignant transformation. Of note, c-MYC gene abnormalities are mainly limited to B-cell lymphoma. T (14, 18) translocation enhances the BCL-2 immunoglobulin heavy chain gene, leading to overexpression of bcl-2 protein and inhibition of apoptosis [31].

This is the second article reporting two DE DLBCL confined to the female genital tract, with one of the patients developing early relapse in the central nervous system in three months. The aim of this study was to remind clinicians of this rare disease, especially the aggressive nature of this neoplasm. However, given the rarity of this entity, very little is known about the roles of these prognostic factors in PLFGT. Therefore, the addition of the new cases may have an important bearing on understanding its clinical characteristics and prognosis. Additionally, for elderly postmenopausal women complaining of abdominal masses, clinicians and pathologists should suspect the possibility of PLFGT in making a more timely diagnosis.

Disclosure of conflict of interest

None.

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