Ultrasound diagnosis and clinicopathological traits of female genital system malignant lymphomas

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Abstract
This study investigated the clinicopathological traits and ultrasound features (including 2-dimensional and color Doppler ultrasound) of female genital system malignant lymphomas and explored the diagnostic performance of ultrasonography in this disease.

Cases of female pelvic lymphoma diagnosed and treated at our hospital between July 2009 and July 2019 were included in this study. Pathological data and ultrasonic manifestations were assessed retrospectively to summarize the clinical traits and ultrasound features of female genital system lymphoma (FGSL). Based on the results, recommendations for ultrasonography-based diagnosis of this disease are proposed.

During the 10-year study period, 20 female patients were diagnosed with malignant lymphomas in the pelvic cavity based on postoperative pathology tests. The age of the patients ranged from 11 to 83 years, and no patients demonstrated specific clinical traits; however, examination of tumor biomarkers revealed that certain patients had elevated levels of CA125. Twenty-eight lesions were identified in the 20 patients, including 24 involving the reproductive system. The primary ultrasonic manifestations were hypoechoic or extremely hypoechoic solid lesions that were relatively large in size, had a relatively regular shape, and had clear boundaries. Certain patients had concurrent ascites, and although some lesions lacked blood supply, most lesions had medium to abundant blood flow, which was largely characterized by low resistance. Almost none of the lesions were definitively diagnosed preoperatively.

Diagnosing malignant lymphomas in the female genital tract remains a considerable clinical challenge. Although certain clinical traits and ultrasound features are associated with this disease and color Doppler ultrasonography might provide vital information indicating the presence of lymphoma, the final diagnosis depends on the clinical and pathological test results of the patients.

Abbreviations: CDFI = Color Doppler flow imaging, DLBCL = diffuse large B cell lymphoma, FGSL = female genital system lymphoma, NHL = Non-Hodgkin lymphoma, NHL-DLBCL = Non-Hodgkin lymphoma-diffuse large B cell lymphoma, RI = resistance index.

Keywords: clinics, genital system, malignant lymphoma, pathology, ultrasonography

1. Introduction
Malignant lymphomas are primarily found in lymph nodes; however, a considerable number of these tumors arise in extranodal lymphoid tissue or infiltrate organs outside of the lymph nodes. Extranodal lymphomas are almost all non-Hodgkin lymphomas (NHLs), which can occur in most organs and tissues and are most commonly found in the gastrointestinal tract.\textsuperscript{1} Extranodal lymphomas are rare in the female reproductive system, accounting for approximately 1% of all cases of lymphomas.\textsuperscript{1} Currently, the preoperative diagnosis rate of malignant lymphomas is extremely low in the female genital tract. This rate is attributed to the lack of distinct clinical signs and inadequate knowledge associated with this disease. Considering these problems, we retroactively analyzed cases of female pelvic lymphoma diagnosed and treated at our hospital between July 2009 and July 2019. Specifically, we analyzed the pathological data and ultrasonic manifestations (including 2-dimensional and color Doppler ultrasound) of these cases and summarize the clinical traits and ultrasonic features of female genital system malignant lymphomas. These findings might help improve our knowledge and diagnosis of this disease.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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2. Methods

2.1. Ethics statement

This study was approved by the Ethics Committee of the West China Second University Hospital, Sichuan University. All patient records and information were anonymized and deidentified prior to analysis.

2.2. Equipment and setting

All examinations were performed using a Philips IU22, IU elite, or HD11 system (Philips, Best, The Netherlands), a GE E8 or Voluson 730 system (GE Healthcare, Waukesha, WI), a Sequoia 512 system (Siemens Healthineers, Germany), or an Esaote Mylab (Esaote, Italy). Transducers included abdominal convex array probes with a frequency of 3.5 to 5.0 MHz and endovaginal probes with a frequency of 5.0 to 7.0 MHz.

2.3. General information

Patients were recruited from the population of patients treated between July 2009 and July 2019 at the Department of Gynecology of West China Second University Hospital, Sichuan University. Based on preoperative ultrasonography, we identified 20 patients who exhibited signs of pelvic cavity swelling. Based on intraoperative observation and postoperative pathology tests, 28 lesions were identified in the 20 patients; 16 patients had lesions in the reproductive system (24 lesions), 3 had intestinal lesions, and 1 had lesions in the left iliac fossa. Only the 16 patients with reproductive system lesions were included in subsequent analyses, and their clinicopathological data and ultrasonic manifestations were examined. The age of these 16 patients ranged from 11 to 83 years, and the mean age was 51.95 years.

2.4. Procedure

For individuals who were sexually active, a combined approach involving vaginal and abdominal ultrasonography was used; for individuals without sexual experience, only abdominal ultrasonography was used. All patients underwent 2-dimensional and color Doppler ultrasonography, and some underwent spectral Doppler detection. Two-dimensional ultrasonography was primarily used to observe the morphology and size of the lesions, internal echo intensity, echo homogeneity, the presence of echo enhancement behind the lesions, the presence of other pelvic and abdominal lesions, and the presence of ascites. Color Doppler flow imaging (CDFI) was primarily used to observe the presence, count, and morphology of blood flow in the lesions. Subsequently, the semiquantitative classification scale of blood flow[23] was used to determine the level of blood flow in the lesions, where 0 represents no sign of blood flow in the lesions, I denotes little blood flow and 1 or 2 sites of dot-like blood flow in the lesions, II represents a medium level of blood flow, one visible main blood vessel whose length surpasses the lesion’s diameter, or the presence of several blood vessels or 3 to 4 dot-like blood vessels; and III represents a high level of blood flow, the presence of >4 blood vessels or an interconnection of vessels that coalesce into a network.

2.5. Statistical analyses

Experimental data were analyzed using SPSS 17.0 (IBM, Almonk, New York). Between-group comparisons were performed using the independent-samples t test and chi-square test, where \( P < 0.05 \) was considered significant.

3. Results

3.1. Diagnostic criteria for primary or secondary lymphoma in the reproductive system

We determined whether a tumor was primary or secondary based on the well-accepted diagnostic criteria for primary lymphomas in the reproductive system,[21] the details of which are as follows: tumors found exclusively or mostly in the female reproductive system, possibly invading neighboring organs or lymph nodes; no tumor cells found in the peripheral blood or bone marrow; distant metastases emerged several months after the discovery of a primary lesion in the female genital tract; no previous history of lymphomas; and lymphoma confirmed on pathomorphological observation. Nine of the 16 patients in this study were diagnosed with secondary lymphomas, and 7 were diagnosed with primary lymphomas.

3.2. Clinical manifestations

The clinical manifestations of the 16 patients lacked specificity. For example, 11 patients had masses palpable in the abdominal or adnexal areas; 5 patients had abdominal bloating with occasional abdominal pain, fever, vaginal bleeding, and changes in stool characteristics; and 1 patient presented with a concurrent breast mass. The clinical traits and pathological diagnoses of the 16 patients are summarized in Table 1.

3.3. Ultrasonographic manifestations

In all, 24 lesions were identified in the 16 patients, including 15 (62.5%; 12 were bilateral in 6 patients) in the ovaries (Fig. 1), 8 (33.3%) in the cervix (Fig. 2), and 1 (4.2%) in the uterus (Fig. 3). Ascites was observed in 7 of the 16 patients (depth, 1.4–7.0 cm). Eleven patients with a total of 16 lesions underwent spectral Doppler detection, which yielded resistance index (RI) values of 0.38 to 0.61. Excluding 1 case diagnosed with metastatic lymphoma, the other 15 cases were not accurately diagnosed preoperatively via qualitative methods. One patient was diagnosed with ovarian epithelial cancer, 1 with dysgerminoma, 1 with endometrial cancer, 3 with cervical cancer, and 1 with cervical fibroids; the remaining case was undetermined. The ultrasonic features of the 16 patients are summarized in Table 2.

4. Discussion

Lymphomas in the female genital system are extremely rare malignancies. Specifically, primary female genital system lymphoma (PFGSL) accounts for only 0.13% of all female reproductive system malignancies.[33] Over the past 3 decades, fewer than 150 cases of female genital system lymphoma (FGSL) have been reported, 59% of which had lesions in the ovary, while 15.5% had lesions in the uterus, 11.5% had lesions in the cervix, 7.5% had lesions in the vulva, and 6% had lesions in the vagina.[33] The 24 lesions in the 16 patients examined in this study involved a total of 15 ovaries (62.5%), and 6 patients had lesions in both ovaries. These findings are consistent with those of previous studies. However, 8 lesions (33.3%) were located in cervix in this study, which is higher than the results of previous...
studies. The sample size and patient age might be the primary reasons for this difference.

Two age ranges have been reported for the peak incidence of FGSL: 10 to 20 years of age and 30 to 40 years of age. These age ranges are younger than those for ovarian cancer, cervical cancer, and lymphomas in other sites. [1] However, the mean age of the 16 patients in this study was 51.95 years, and patients older than 45 years accounted for 62.5% of the sample, which is inconsistent with previous studies. We speculate that the inconsistency may have resulted from the small sample size and the uneven age distribution.

Patients with FGSL lack distinct clinical symptoms. Most patients exhibit only general signs such as bloating, lower back pain, and a palpable pelvic mass, whereas approximately 17% of patients develop fever, night sweats, and decreased body weight. Consequently, the disease is difficult to distinguish from other types of pelvic tumors. [4] In addition, this disease is rare, resulting in inadequate knowledge among clinicians and

| No. | Age, y | Lesion sites discovered intraoperatively | Tumor markers, U/mL | Histological type |
|-----|--------|-----------------------------------------|---------------------|------------------|
| 1   | 63     | Left ovary | CA19-9 30.86 | A propensity of T cell diffuse large B cell lymphoma (DLBCL) |
| 2   | 50     | Left ovary, cervix, left fallopian tube, pelvic cavity | CA125 437.6, CA125 70.10 | NHL-DLBCL |
| 3   | 38     | Left and right ovaries | CA125 238.1 | NHL, involvement of mostly systemic anaplastic large cell lymphoma (might originate from activated mature cytotoxic T cells) |
| 4   | 71     | Cervix | CA19-9 30.7 | DLBCL |
| 5   | 25     | Left and right ovaries | CA125 212.6 | Diffuse, consistent infiltration by medium-to-large lymphoid cells, NHL suspected |
| 6   | 11     | Left and right ovaries | CA125 1823.4 | B cell-derived NHL, tumor involvement of the right fallopian tube (secondary) |
| 7   | 73     | Uterus, cervix, left and right ovaries, left fallopian tube, bowel | | DLBCL |
| 8   | 83     | Cervix | | DLBCL |
| 9   | 72     | Cervix | | DLBCL |
| 10  | 25     | Left and right ovaries | CA125 174 | B cell-derived NHL (primary) |
| 11  | 40     | Cervix | | NHL-DLBCL |
| 12  | 35     | Left ovary | CA19-9 19.0 | NHL-DLBCL (secondary) |
| 13  | 70     | Left ovary | Negative | B cell lymphoma |
| 14  | 62     | Cervix | | B cell lymphoma |
| 15  | 64     | Left and right ovaries, cervix | | B cell-derived NHL |
| 16  | 71     | Uterus, cervix, vagina | CA125 83.2, CA19-9 20.1 | DLBCL |

DLBCL = diffuse large B cell lymphoma, NHL = Non-Hodgkin lymphoma, NHL-DLBCL = Non-Hodgkin lymphoma-diffuse large B cell lymphoma.

Figure 1. Sonographic images of the lesions in the ovary. (A) 2D ultrasound demonstrating a heterogeneous hypoechoic mass with a nearly oval shape in the right posterior portion of the uterus. Ascites were visible around the mass. (B) CDFI showed abundant blood flow of level III in the lesion. 2D = two-dimensional; CDFI = color Doppler flow image; M = mass; UT = uterus.
imaging specialists as well as a poor rate of preoperative diagnosis. In this study, we analyzed the clinicopathological traits and ultrasonic manifestations of the patients and compared them with those in relevant literature.\[^{[1,3–7]}\] We summarized the characteristics of FGSL, the details of which are described below, to increase our understanding of the disease. First, this disease lacks any distinct clinical symptoms, and only slight to medium elevation of the tumor biomarker CA125 was observed. In this study, 7 patients exhibited an increased CA125 level (range, 70.1–437.6 U/mL for 6 patients; 1823.4 U/mL for 1 11-year-old patient). Second, the disease is characterized by the following ultrasonic features: large solid masses with relatively regular shapes and clear boundaries present in the adnexal area or cervix. These masses were uniformly hypoechoic; however, certain lesions exhibited almost no echo, although echo enhancement might appear in the back of the lesions. Degenerative necrosis-induced liquefaction or calcification was rarely found inside the lesions. Alternatively, uterine lesions manifested relatively uniform echoic reduction in the uterine muscle, but no apparent abnormalities were found with respect to endometrial morphology or echo. We speculate that these unexpected signs are due to several traits of lymphoma cells, that is, their diffuse distribution, similar cell sizes, lack of cell type diversity, and expansion growth (which is the primary means through which these cells grow). In addition, few patients had concurrent ascites. Third, CDFI revealed a medium to abundant level of blood flow in most lesions. In this study, 20 of the 24 lesions (83.3%) exhibited blood flow of level II or above. Spectral Doppler mostly revealed low-resistance arterial blood flow and an RI range of 0.38 to 0.61 among the 16 lesions examined. Based on the well-accepted diagnostic criteria for PFGSL\[^{[2]}\] 9 cases of secondary lymphoma and 7 cases of primary lymphoma were diagnosed. However, no apparent differences were observed between the 2 types in terms of

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**Figure 2.** Sonographic images of the lesions in the cervix. (A) 2D ultrasonic sagittal view of the uterus demonstrating that the cervix was obviously enlarged and presented a regular, well-defined hypoechoic mass that was significantly lower than the uterine echo. (B) CDFI showed abundant blood flow of level III in the lesion. 2D = two-dimensional; CDFI = color Doppler flow image; M = mass; UT = uterus.

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**Figure 3.** Sonographic images of the lesions in the uterus. (A) Transabdominal 2D sagittal view of the uterus demonstrating that the echo of the entire uterus is hypoechoic but the uterine cavity is normal except for effusion. (B) Transvaginal sagittal view of the uterus of the same patient demonstrating that the lesions involved the entire uterus and presented a relatively homogenous hypoechoic mass. CDFI showed sparse blood flow of level II in the lesion. CDFI = color Doppler flow image; CX = cervix; UT = uterus.
clinical symptoms or ultrasonic alterations; thus, imaging cannot be used to preoperatively distinguish these tumors.

Moreover, we noticed that the distribution of ovarian lesions among young and old people was similar, and cervical lesions were primarily found in elderly patients. In this study, no cervical lesions were found in patients younger than 40 years. Currently, the pathogenic mechanisms of genital system lymphoma are not fully understood, although the disease might be related to stimulation of inflammation, chronic proliferation of lymphocytes, and the presence of autoimmune diseases.[5] After childbirth, women have a higher incidence of cervicitis compared with uteritis (uterine inflammation) and adnexitis (adnexal inflammation). Younger people have a lower likelihood of a pathogenic influence on the cervix. We presume that these differences might be the reason that elderly people have a higher incidence of cervical lymphoma than their younger counterparts. Of course, because of the small sample size of this study, the results might be biased. Whether the age distribution of cervical lymphoma conforms to this rule must be studied in larger samples.

In the case of ultrasonic diagnoses, PFGSL must be distinguished from other reproductive system malignancies. Ovarian lymphoma should be differentiated from other ovarian tumors. These tumors might include ovarian epithelial tumors, ovarian germ cell tumors, or ovarian metastatic tumors. Unilateral lesions are more common in ovarian epithelial tumors, and the ultrasonic manifestations primarily include adnexal cystic and solid masses, most of which have unclear boundaries and irregular shapes and are often accompanied by extensive ascites and a significantly elevated level of CA125 (often >500 IU/mL). Specific markers of ovarian germ cell tumors (e.g., AFP) can be increased, and patients often present with menstrual changes due to the endocrine function of tumors. The primary lesions found in the gastrointestinal tract or breast are a prominent feature of metastatic ovarian tumors. Likewise, cervical lymphoma should be differentiated from cervical cancer. Compared with cervical cancer, cervical lymphoma has a lower echo, a more uniform internal echo, and clearer lesion boundaries, and most do not destroy the cervical canal. In addition, uterine lymphoma is caused by the infiltrating growth of intrauterine neoplasm cells, which leads to a uniformly lower echo, less invasion of uterine and endometrial structures, and no obvious changes in endometrial morphology or echo. This condition can be differentiated from uterine sarcoma and endometrial cancer.

It is worth paying attention to that the gold diagnostic standard is still the postoperative pathological diagnosis, although FGSGL has certain ultrasonic characteristics. Diagnosis based merely on the ultrasound findings may lead to overdone. Suspected lymphoma by operators based on the gross feature during the operation and frozen report by pathologists might be a key factor to appropriately diagnose FGSGL.

In summary, FGSGL is a low-prevalence malignancy that lacks distinct clinical symptoms. If uniform echo reduction in the uterus or hypoechoic masses with clear boundaries and regular shapes are observed on ultrasound, then the possibility of lymphoma should be carefully considered. In these cases, further assessments should be performed to enhance the accuracy of the preoperative diagnosis of this disease.

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Author contributions

Conceptualization: Min He.
Data curation: Min He.
Statistical analysis: Sha Hu.
Writing – original draft: Min He.
Writing – review & editing: Hong Luo.

Corrections

In the abstract, NHL was incorrectly defined as q lymphoma, it has now been corrected to non-Hodgkins lymphoma. The sentence “MH and SH contributed equally to this work” has been deleted. Department of Ultrasound has been added to the corresponding author details. (IBM, Almonk, New York) has been added to the SPSS details. In table 1, the negative symbol before the 6 in the first column has been removed and the B has been added before the Cell-derived NHL in the fourth column. Under the Author Contributions, Sha Hu has been changed to Min He for Data curration and Formal analysis was changed to Statistical analysis.

References

[1] Jiang XF, Yang KX, Peng Z, et al. Clinicopathologic and immunohistochemical study of primary non-Hodgkin lymphoma of the female genital system. Chin J Obstet Gynecol 2007;42:222–6.
[2] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375–90.

[3] Anagnostopoulos A, Mouzakiti N, Ruthven S, et al. Primary cervical and uterine corpus lymphoma; a case report and literature review. Int J Clin Exp Med 2013;6:298–306.

[4] Chen R, Yu Z, Zhang H, et al. Primary malignant lymphoma of the uterus and broad ligament: a case report and review of literature. OncoTargets Ther 2015;8:265–8.

[5] Binesh F, Vahedian H, Rajabzadeh Y. Primary malignant lymphoma of the uterine cervix. BMJ Case Rep 2012;2012:bcr 2012006675.

[6] Kasai M, Ichimura T, Murakami M, et al. Two cases of uterine malignant lymphoma diagnosed by needle biopsy. J Obstet Gynaecol Res 2015;41:1664–8.

[7] Kosari F, Daneshbod Y, Parwaresch R, et al. Lymphomas of the female genital tract: a study of 186 cases and review of the literature. Am J Surg Pathol 2005;29:1512–20.