Learning objectives

To perform a pictorial essay reviewing ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) features of primary gynaecological lymphoma.
Background

Primary lymphomas of the female genital tract are very rare and account to less than 1% of extra-nodal malignant lymphomas (1). Secondary involvement, although uncommon, is more frequently found. The uterine cervix is the most common primary location in the genital tract, whereas the ovary constitutes the most common secondary site of lymphomatous involvement (2).

Lymphomas occurring in the female reproductive system are typically diffuse large B-cell non-Hodgkin's lymphomas (NHLs) (3). Etiology and pathogenesis of primary genital tract NHLs are unknown, despite there might be a possible association between chronic inflammation and lymphomas (4).

The diagnosis of a primary lymphoma implies the existence of some criteria:

- First, at the time of diagnosis, the disease has to be confined to a solitary extra-nodal site, an adjacent lymph node group, or other contiguous structures;

- Second, no abnormal cells should be found in the peripheral blood and bone marrow. In the case of the diagnosis of lymphoma, bone marrow biopsy must follow to exclude leukaemia;

- Finally, other lymphomatous lesions should not appear at distant locations several months after the initial diagnosis.

In fact, if these stringent criteria are used, primary malignant lymphomas of the female genital tract will be very rare (1,2,5).

The clinical presentation of primary gynaecological lymphomas is non-specific and depends on the involved organ and tumour aggressiveness. Vaginal bleeding and discharge may happen in uterine and vaginal lymphomas. Other manifestations, like abdominal mass, dyspareunia, perineal discomfort, and urinary retention, may appear in lymphomas from several locations and depends on the tumour size, compressive effects and invasion of contiguous structures. Constitutional symptoms are common.

The imaging approach of gynaecological lymphomas is also non-specific. US, CT, and MRI are the usual performed techniques. US must combine transabdominal and transvaginal approaches and remains very useful in the initial management of adnexal, endometrial and myometrial lesions. CT is frequently used for staging purposes, but it may be also required to target and guide biopsies of suspicious masses and nodes, especially if they are deep and inaccessible to ultrasound guidance. Because of its high
soft tissue resolution, MRI constitutes the most accurate tool to evaluate pelvic masses. It is not only useful for characterizing undetermined adnexal masses, but also allows a much better differentiation between normal tissue and tumour, which helps on local staging (6).

Scintigraphic studies, positron emission tomography (PET) and PET-CT appear to be valuable in the identification of disease in non-enlarged organs, residual tumour (versus post-treatment fibrosis), and early recurrence.

It should be emphasized that, unlike other primary tumours, staging of lymphomas of the female genital tract is based on the Ann Arbor system and not on FIGO (International Federation of Gynecology and Obstetrics) staging.

The prognosis of lymphomas of the female genital tract is variable and depends on the stage and histological subtype. Primary lymphomas tend to have better prognosis when compared to secondary involvement (7).

Because of the low incidence of gynaecological lymphomas, there is no widely accepted consensus on its management. However, the correct diagnosis of lymphoma and the subsequent adequate staging are crucial in order to avoid unwarranted surgeries or therapies that would be acceptable for other non-lymphomatous tumours. Therapy choices for gynaecological lymphomas are variable and consist of irradiation alone or irradiation with either surgery or chemotherapy (4,8).

We present a review of the general imaging findings of gynaecological lymphomas, focusing on the ovaries, uterus and vagina. Lymphomas of the fallopian tubes and vulva are particularly rare and will not be separately discussed.
Findings and procedure details

General Imaging Findings

Despite not being specific, some imaging features may raise the suspicion of lymphomatous disease:

- In nodular and multinodular lymphoma, it is expected to find solid, well-defined, and homogeneous masses;

- Diffuse lymphomas tend to enlarge but structurally preserve the involved organs;

- The presence of necrosis is uncommon, unless fast growth or chemotherapy had occurred. Haemorrhage and calcification are also rare but may be seen after treatment;

- Lymphomas tend to be mildly vascularized and generally do not show avid enhancement after contrast administration on CT or MRI;

- Regional nodal involvement may be suggestive of lymphoma, so the knowledge of the most suitable routes of nodal dissemination is crucial.

Ovary

Malignant lymphomas often involve the ovaries at necropsy or autopsy with a frequency ranging from 7 to 26%, depending on the studies. However, less than 1% of patients with malignant lymphoma initially present with ovarian enlargement or clinical signs (9).

Primary ovarian NHL accounts for 0.5% of all NHLs and 1.5% of all malignant ovarian neoplasms (5,10). The most common types are diffuse large B-cell, Burkitt and follicular lymphomas. Some authors think that primary ovarian NHL may arise from hilar lymphoid tissue or teratomas (5,7).

The patients have a wide age range, but are generally premenopausal and present with pelvic or abdominal complaints. Nevertheless, some ovarian lymphomas appear as incidental findings arising in unusual settings, such as within the wall of an ovarian endometriotic cyst or associated with other tumours (mature cystic teratoma and serous borderline tumour were already described) (10).

In 50% of the cases, ovarian lymphomas are bilateral, large, and solid tumours. Despite bilaterally has been associated to disseminated disease, some primary bilateral ovarian
lymphomas were already reported. Ovarian lymphomas tend to maintain an intact capsule and not to distort the organ architecture. Ascites and peritoneal implants are not usually found (7).

Ultrasonography usually shows homogeneous, hypoechoic tumours without posterior acoustic enhancement (5). On CT, ovarian lymphomas appear as well defined, solid masses with mild contrast enhancement. On MRI, they show an intermediate signal on T1WI, low to intermediate signal on T2WI, and mild contrast enhancement. Internal hyperintense septa and peripheral follicles on T2WI were also reported (11).

The finding of an ovarian solid tumour on imaging studies implies the consideration of other diagnosis besides lymphoma, essentially if no suspicious nodes are found. Serous, undifferentiated, and borderline tumours may be bilateral and mimic lymphomas, although they tend to be associated with ascites and display a more heterogeneous architecture, with solid and cystic portions. Metastases should also be cogitated, despite they generally display avid contrast enhancement and central areas of necrosis. Other solid tumours may have a similar presentation, either malignant like dysgerminoma and Sertoli-Leydig, or benign like fibroma, thecoma and Brenner cell tumour (7).

The histological diagnosis may be also challenging. The distinction between ovarian lymphoma and dysgerminoma may be particularly difficult since they share macroscopic and histological features. Granulocytic sarcoma, undifferentiated carcinoma, small carcinoma of the hypercalcemic type, and metastatic breast carcinoma should also be considered in the histological differential diagnosis (7).

The question of whether some ovarian lymphomas can be considered truly primary or the initial manifestation of a generalized disease is not easy to answer. However, this distinction appears to be important in terms of prognosis (9). The initial clinical manifestation of an occult nodal lymphoma as an ovarian mass is known as having a poor outcome with a survival rate ranging from 7% to 38% at 5 years, when compared to a primary ovarian lymphoma, which typically has better prognosis (5, 10).
**Fig. 1**: Secondary involvement of the ovaries (A and B) and the cervix (C) by Burkitt lymphoma. Both ovaries are homogeneously enlarged and maintain their echogenicity and architecture. A round, hypoechoic, nodule is also found in the cervix (arrow).

**References**: Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT
**Fig. 2:** Bilateral primary non-classifiable B-cell lymphoma of the ovaries. Axial T2WI (A), axial T1WI (B), axial contrast-enhanced fat-saturated T1WI (C), sagittal T2WI (D), and coronal T2WI (E). Bilateral, large, lobulated, solid, and globally homogeneous adnexal mass showing low signal intensity on T1WI and intermediate signal intensity with some hyperintense septa (arrowhead) on T2 WI. The uterus is displaced to the right (asterix) and the iliac vessels are laterally displaced (arrows). Mild and homogeneous enhancement is found in the majority of the tumour after gadolinium administration. Some septa display avid enhancement (arrowhead). Small amount of ascites is found in the cul-de-sac and both paracolic gutters. The gross findings obtained after laparotomy show the right (F and G [midline section]) and left (H) ovaries totally replaced by solid, compact, and lobulated tumours.

**References:** Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT
Primary malignant lymphomas of the uterus are rare. Most lymphomas involving the uterine corpus and the cervix are secondary and concern non-Hodgkin lymphoma, usually of the diffuse large B-cell type (1). Follicular lymphoma, Burkitt lymphoma and T-cell lymphoma can also occur in the uterine corpus, while MALToma and Burkitt lymphoma have already been described in the cervix (2,7,12).

Similar to other uterine tumours, the patients typically present with menorrhagia, metrorrhagia, irregular menses, post-coital bleeding, post-menopausal bleeding, and other forms of dysfunctional uterine bleeding or discharge. Abdominal or pelvic pain, dyspareunia, and mass effect were also reported (1,13). Some cervical lymphomas are incidentally detected on routine Papanicolaou cytologies (12). However, some lymphomas are subepithelial and, unless ulceration or exfoliation is present, Papanicolaou smear plays a minor role in the diagnosis (4).

The imaging features of uterine lymphomas are also non-specific and may simulate other tumours. However, the uterine corpus usually shows symmetrical, diffuse infiltration and enlargement, with preservation of the uterine architecture and normal endometrial enhancement on MRI. Some nodular lymphomas may mimic intramural or submucosal leiomyoma (1,4).

The cervix is typically enlarged and barrel-shaped, although polypoid or nodular masses may also be found. Cervical lymphoma displays low signal intensity on T1WI and high signal intensity on T2WI, resembling cervical squamous cell carcinoma. However, lymphomas are large and non-necrotic, and typically do not infiltrate surrounding structures (1,5). MRI also allows the visualization of an intact mucosa, which seems to be distinctive of lymphoma (6).

If present, the pattern of regional nodal involvement may be helpful, since these nodes tend to be large, homogeneous and non-necrotic.

The histopathological diagnosis may be particularly challenging in the lymphomas of the uterine corpus. The differential diagnosis should include atypical lymphoma-like inflammatory lesions of the endometrium and uterine leiomyomas massively infiltrated by lymphocytes. The imaging approach does not allow this differentiation (7).
**Fig. 3:** Primary diffuse large B-cell NHL of the uterine corpus and cervix. Axial (A) and sagittal (B) non-enhanced CT of the pelvis. Diffuse and homogeneous enlargement of the uterine corpus and cervix. A right external iliac adenopathy is also seen (arrow).

**References:** Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT
Fig. 4: Primary diffuse large B-cell NHL of the endometrium. Axial non-enhanced CT of the pelvis (A), sagittal T2WI (B), axial T1WI (C), and axial contrast-enhanced fat-saturated T1WI (D). CT shows a homogeneous pelvic mass that mainly occupies the uterine corpus, extends to the right parametrium, encases the homolateral ureter (white arrowheads), and invades the posterior pelvic wall (white arrows). MRI better depicts the mass, identifying a polypoid tumour that is placed in the endometrial cavity and extends to the myometrium, cervix, anterior vaginal wall and posterior bladder wall (red arrowhead). This tumour is hypointense on T1WI, moderately hypertintense on T2WI, and shows uniform, mild enhancement after gadolinium administration. Both CT and MRI show enlarged lymph nodes (red arrows).

References: Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT

Vagina

Patients with primary or secondary lymphomas of the vagina usually present with vaginal bleeding, but in some cases a mass is seen on clinical examination. The majority of
vaginal lymphomas are diffuse large B-cell NHL. Lymphomas of the vagina are most commonly infiltrative and display diffuse thickening, often with contiguous extension into the cervix. Similar to cervical lymphoma, an intact mucosa appears to be characteristic. These features are possible to identify on MRI, which should be performed after filling the vagina with gel (7).

**Fig. 5**: Primary B-cell NHL of the uterine cervix and vagina. Axial of the cervix (A and B) and sagittal T2WI (C), axial of the cervix (D) and sagittal contrast-enhanced fat-saturated T1WI. The vaginal wall is slightly hyperintense and diffusely thickened. Note the particular thickening of the posterior fornix (arrowheads) and the infiltration of both ureters (arrows). The tumour display diffuse and homogeneous enhancement.

**References**: Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT
**Fig. 6:** Primary diffuse large B-cell NHL of the vagina. Axial (A and B) and sagittal (C) T2WI. Large, lobulated pelvic tumour, mildly hyperintense on T2WI, involving the vagina, and displacing the uterus superiorly (red arrow), the bladder anteriorly and the sigmoid colon posteriorly. The tumour invades the left posterior pelvic wall and the perineum (asterix). Internal iliac lymphadenopathies are also seen (white arrows).

**References:** Department of Radiology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon/PT
Conclusion

The imaging features of lymphomas of the female genital tract are non-specific and mimic other tumours. The definitive diagnosis is obviously histological, but some distinctive imaging features may raise the suspicion of lymphomatous disease:

- The involved organs tend to be enlarged but preserve their structure;

- The tumours are homogenous, non-necrotic in the absence of treatment, and show mild vascularization;

- Despite large, these tumours generally are circumscribed to the organ of origin and do not invade adjacent structures (for example, ovarian lymphomas typically present without ascites, and lymphomas of the uterine corpus and cervix tend to spare the junctional zone and inner stromal layer, respectively);

- The pattern of nodal involvement may be also helpful: these lymph nodes are typically homogeneous and non-necrotic.

The distinction between lymphomatous and non-lymphomatous tumours is crucial, since complementary diagnostic management, staging systems, and treatment choices are different. Moreover, primary and secondary lymphomas may also be distinctly treated and should be differentiated. In this set, the recognition of distant metastases or non-contiguous enlarged lymph nodes at the time of the diagnosis or several months after it, is indicative of disseminated, secondary involvement.

So, the currently used imaging tools may detect suspicious features of lymphoma, give a provisional diagnosis, stage the disease, and also guide the biopsy of nodes and masses.
Personal information

João Lopes Dias
Department of Radiology
Hospital de S. José
Portugal

Teresa Margarida Cunha
Department of Radiology
Instituto Português de Oncologia de Lisboa Francisco Gentil
R. Prof. Lima Basto
1099-023 Lisboa
Portugal
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