BMC Women's Health

CASE REPORT Open Access

Aggressive primary uterine non-Hodgkin's lymphoma presenting as acute kidney injury: a case report

Rawan Al-Deeb[1*], Ram Attaf[2], Yaman Saiouf[3], Baraa Mouzi[3,4] and Assef Dayyoub[5]

Abstract

Introduction Primary malignant lymphoma of the cervix is an extremely rare condition, accounting for only 0.008% of all cervical tumors and 2% of female extranodal lymphomas. The most common histological subtype is diffuse large B-cell lymphoma. This malignancy is often asymptomatic in its early stages, but advanced cases may include systemic symptoms, pelvic discomfort, and vaginal bleeding. Diagnosis is challenging due to its nonspecific clinical presentation and similarity to other gynecological conditions. Imaging and immunohistochemistry play essential roles in diagnosis and staging. Treatment typically involves chemotherapy, with the standard CHOP regimen for Non-Hodgkin's lymphoma being the main treatment in most cases. To the best of our knowledge, this is the first case in the literature to describe acute kidney injury associated with the already rare entity of primary female genital tract lymphoma.

Case presentation A 66-year-old multiparous woman presented with severe headache, nausea, vomiting, and dizziness lasting three days, alongside systemic symptoms such as weight loss, lethargy, and night sweats. Imaging indicated bilateral hydronephrosis, ascites, and an enlarged uterus with a suspected tumor. Biopsy confirmed diffuse large B-cell lymphoma with immunohistochemical positivity for CD20 and negative CD3. The patient was classified as stage IV according to the Ann Arbor system. Initial treatment included diuretics, hemodialysis, and chemotherapy with a dose-reduced CHOP regimen due to atrial fibrillation and reduced cardiac ejection fraction. Despite initial improvements, the patient developed tumor lysis syndrome and meningeal infiltration. Her condition deteriorated after the second chemotherapy cycle, culminating in neutropenic fever, massive hemorrhage, and ultimately death.

Conclusion Our case highlights the diverse manifestations of the disease, including acute kidney injury secondary to bilateral hydronephrosis, a previously unreported complication. Early recognition is essential for optimal management. While chemotherapy remains the mainstay of treatment, the lack of standardized protocols underscores the need for further research. This case emphasizes the unpredictable nature of primary female genital tract lymphomas and their potential to cause systemic complications.

Keywords Extranodal non-Hodgkin's lymphoma, Primary female genital tract lymphoma, Primary uterine lymphoma, Case report

*Correspondence:
Rawan Al-Deeb
rawanaldeeb484@gmail.com
[1]Faculty of Medicine, Homs University, Homs, Syrian Arab Republic
[2]Al Andalus University for Medical Sciences, Tartus, Syria
[3]Faculty of Medicine, Damascus University, Damascus, Syrian Arab Republic
[4]Department of Oncology, Al-Bairouni Hospital, Damascus, Syrian Arab Republic
[5]Faculty of Medicine, Department of Oncology, Al-Bairouni Hospital, Damascus, Syrian Arab Republic

Background

Non-Hodgkin lymphoma (NHL) affects extra-nodal regions in approximately one-third of patients, with the female genital tract being among the areas impacted [1].

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent and aggressive form of non-Hodgkin lymphoma, representing around 30–40% of all cases [2].

The epidermis and gastrointestinal tract are prominent extranodal sites [3].

However, it is uncommon for the uterus and reproductive organs to be involved, and this occurrence has not been well documented. Primary lymphomas in the female genital tract account for only 0.2–1.1% of all extranodal lymphomas. In most instances, uterine lymphoma results from secondary involvement of the disease [2].

The Ann Arbor staging method is used to classify pelvic lymphomas; depending on the tumor location, symptoms of more advanced stages include vaginal bleeding or discharge, stomach distension, bloating, and pelvic discomfort. In the early stages, women are frequently asymptomatic. It is uncommon for extranodal lymphomas to exhibit constitutional "B" symptoms, such as fever, asthenia, night sweats, and weight loss [4].

Because of its rarity, NHL involving the uterus may be challenging for pathologists to diagnose if they are not familiar with the clinicopathologic features of the condition there [3].

In the absence of standardized protocols, the majority of studies advocate for a multimodal treatment strategy that encompasses chemotherapy- specifically, the cornerstone regimen consisting of cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP)—in conjunction with surgical intervention and radiotherapy [4].

Here we report an interesting case of an aggressive non-Hodgkin's lymphoma localized to the uterine region presenting as acute kidney injury.

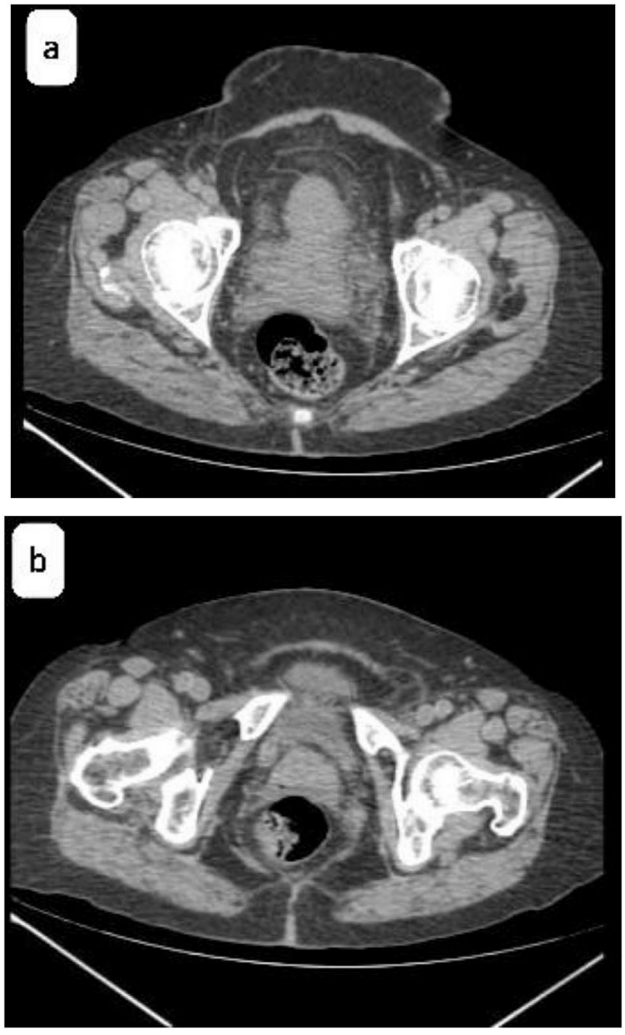

Fig. 1 (**a**, **b**) Axial computed tomography (CT) of the pelvis displaying the mass and accompanying edema

Case presentation

A 66-year-old multiparous woman presented with a three day history of severe headache, nausea, vomiting, respiratory distress, and dizziness. She reported a history of weight loss, loss of appetite, lethargy, and severe night sweats, along with psychological distress lasting approximately two weeks.

Her past medical history included a myocardial infarction treated with medication. There was no relevant family history. On physical examination, abdominal and pelvic examination were not noteworthy. Cervical examination revealed diffuse edema and enlargement of the cervix.

Initial laboratory tests showed elevated levels of creatinine, blood urea, uric acid, phosphorus, and CRP, along with decreased red blood cell count, hemoglobin, and platelet count. ESR in the first hour and beta-2 microglobulin levels were also high.

A multi-slice computed tomography (CT) scan of the abdomen and pelvis revealed an enlarged right (approximately 13.5 cm) and left kidney (approximately 13.7 cm) with negative cortical dedifferentiation and surrounding fat infiltration, indicating bilateral hydronephrosis without evidence of nephrolithiasis due to bilateral ureteral compression There was evidence of first-degree ascites, generalized fatty infiltration of the abdomen, and a small amount of free fluid in Morrison's pouch and the pelvis. The uterus appeared enlarged with fluid exudation into its cavity, with a lesion consistent with a tumor warranting further follow-up and investigation (Figs. 1 and 2).

The patient was initially treated with diuretics and intravenous fluids. Hemodialysis was initiated due to persistent hyperacidosis due to post-renal acute kidney failure caused by compressive uropathy, as shown on CT

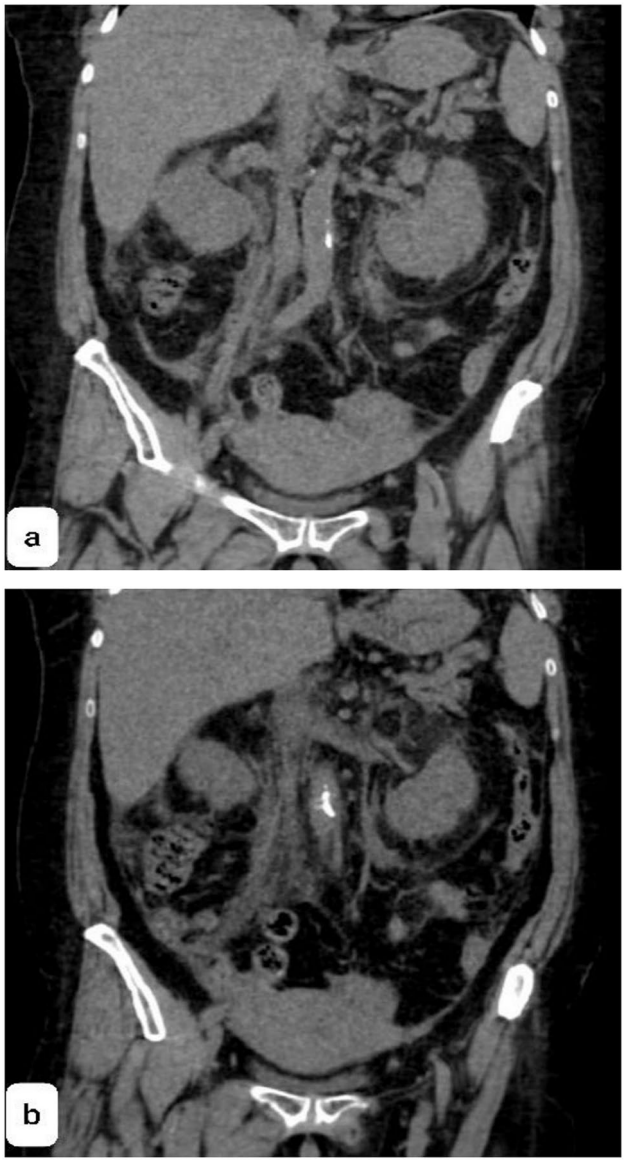

Fig. 2 (**a**, **b**): Coronal plain views of computed tomography (CT) abdomen scans displaying enlarged uterus, edema, and bilateral enlargement of the kidneys due to ureteral obstruction by the mass

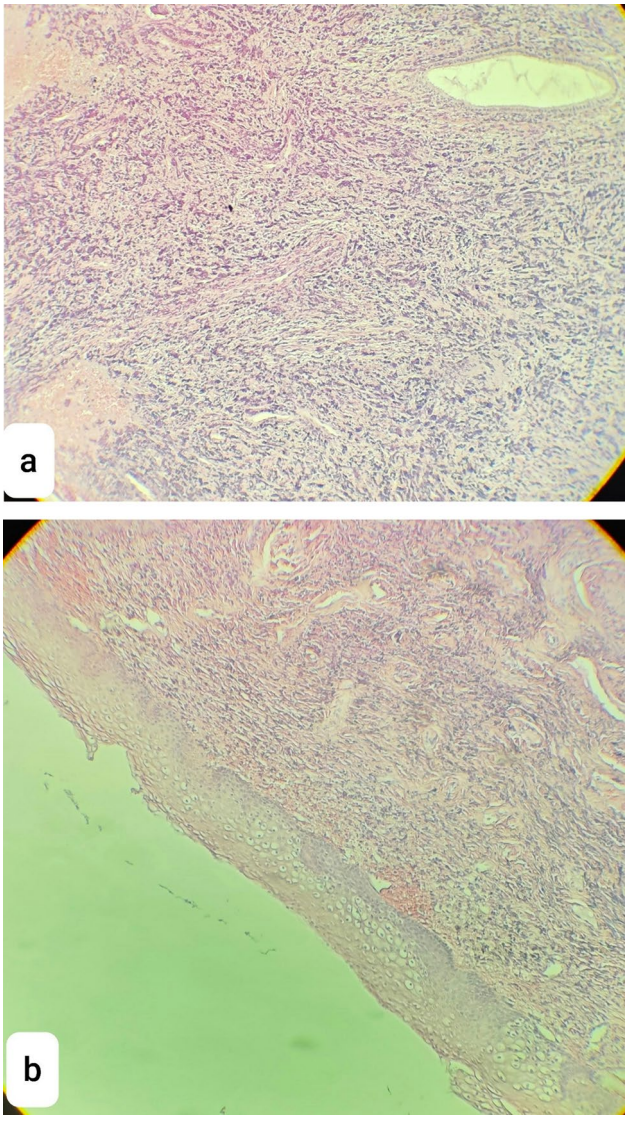

Fig. 3 (**a**, **b**): Cervical biopsy results displaying lymphocytic infiltrate in line with diffuse large B-cell lymphoma (DLBCL) of the cervix

scans. Cervical biopsy revealed diffuse large B-cell lymphoma with high mitotic activity according to WHO classification [5]. (Fig. 3)

According to the Ann Arbor classification, the patient was diagnosed with stage IV Non-Hodgkin's lymphoma. Immunohistochemistry (IHC) studies demonstrated positivity for CD20, while CK and CD3 were negative (Fig. 4).

Unfortunately, due to lack of access, we could not perform a more detailed immunohistochemical panel.

Pleural fluid biopsy smears indicated a prominent density of large lymphocytes with high mitotic activity and a few reactive mesothelial cells. The recommended chemotherapy regimen was CHOP (cyclophosphamide 650 mg/m^2, doxorubicin 50 mg/m^2, oncovin 1 mg/m^2, and prednisolone 100 mg for 5 days every 3 weeks).

However, the day before the first dose, the patient experienced atrial fibrillation, and her ejection fraction decreased from 66 to 40%, necessitating a 50% dose reduction with slow infusion.

Despite initial clinical improvement, including resolution of respiratory distress and increased urinary output, laboratory tests indicated tumor lysis syndrome. After appropriate treatment with intravenous fluids, laboratory values returned to normal limits. Three days later, the patient experienced a severe headache. A brain scan ruled out metastases. Subsequently, a lumbar puncture was conducted to analyze the cerebrospinal fluid, which demonstrated evidence of meningeal tumor infiltration. After the second dose of chemotherapy, the patient's

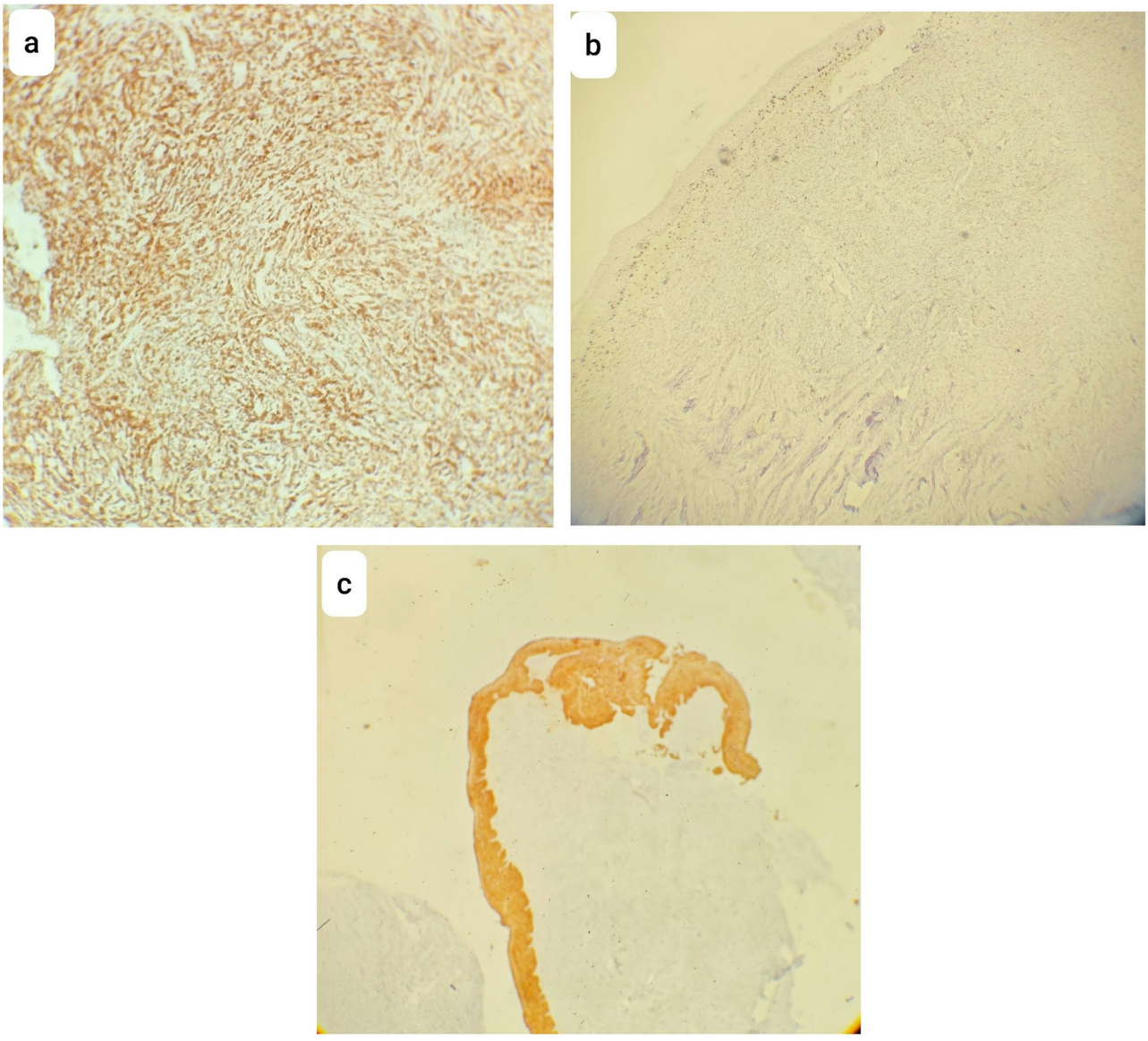

Fig. 4 Immunohistochemical staining of the cervical biopsy showing positivity for CD20 and negativity for CK and CD3 (**a**:CD20, **b**: CD3, **c**: CK)

overall condition deteriorated, and she developed neutropenic fever and a massive hemorrhage, which ultimately led to her death.

Discussion and conclusions

Non-Hodgkin lymphoma (NHL) rarely affects the female genital tract, with primary cases representing 0.2 to 1.1% of all extranodal NHLs [6]. In a study of 697 cases, the most common sites of primary female genital tract lymphomas (PFGTL) were the ovary, cervix, and uterus, respectively [7]. PFGTL is typically diagnosed in the 5th decade, with patient age ranging from 20 to 80 years [8], though it is more common among postmenopausal women [1].

Female genital tract lesions are more frequent in disseminated disease and remain extremely rare as primary cases [1]. The distinction between primary and secondary extranodal lymphomas remains unclear, with some authors relying on the presence of systemic symptoms and signs to do so [3, 9].

Due to the lack of a conclusive definition, case-by-case investigation is critical to correctly diagnose and treat patients [7].

In early stages, PFGTL patients are usually asymptomatic [6]. Eventually, patients may develop distension and gynecological symptoms such as abnormal uterine bleeding (AUB) [7]. Systemic symptoms, including weight loss, anemia, and generalized lymphadenopathy are more common in disseminated disease [3, 10]. Large tumors

may compress nearby organs, causing uterine prolapse, dysuria, urinary frequency, urinary retention or rectal urgency [3, 4, 11].

The most common subtype of PFGTL is diffuse large B-cell lymphoma (DLBCL), with more rare types including Hodgkin's lymphoma, T-cell lymphomas, and MALTomas [6, 9]. Nasioudis et al. found that DLBCL constituted almost 60% of cases, followed by follicular and Burkitt lymphoma, respectively [7]. Ahmad et al. found that non-B-cell lymphomas carry a worse prognosis compared to B-cell variants [12].

Thus, immunohistochemistry presents a diagnostic cornerstone, though no single marker is specific for DLBCL of the female genital tract [10]. In our case, pathological examination confirmed DLBCL (Figure. 3), with CD20-positive tumor cells and negative CD3 among reactive lymphocytes. (Figure. 4) Access to more advanced immunohistochemical studies, such as those forming the Hans algorithm, CD10, BCL-6, and MUM-1, would have been beneficial for accurately establishing tumor subtype and subsequent treatment and prognosis [10].

Due to the rarity of PFGTL and its nonspecific presentation, physicians frequently misdiagnose PFGTL as other tumors, such as epithelial or endometrial stromal tumors [6, 10]. The differential diagnosis of PFGTL includes carcinomas, uterine sarcomas, and malignant mixed mullerian tumors, among other tumors [3].

Imaging investigations, such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) play a limited role in diagnosis, yet they provide valuable information for staging and surgical planning [4, 9]. On US, cervical lymphomas are lobulated, usually well-vascularized masses [4]. MRI can differentiate between uterine sarcoma and PFGTL, as the former has a uniform signal intensity on MRI, while the latter is hypointense on T1-weighted images and hyperintense on T2-weighted images [1]. In our case, computed tomography revealed an enlarged uterus with fluid accumulation in its cavity, along with a mass lesion warranting further investigation.

Furthermore, the lack of cervical epithelial involvement in cervical lymphoma and myometrial invasion in uterine lymphoma presents a possible clue towards PFGTL [1].

CT can detect metastases and lymphadenopathies, while PET-CT is key for staging as well as monitoring treatment response. Notably, cervical, uterine, and vaginal lymphomas do not alter the zonal architecture of the organ, providing physicians with a clue towards the diagnosis [10].

Differentiating PFGTL from reactive lymphoid hyperplasia, such as chronic or follicular cervicitis and papillary endocervicitis, can be challenging. Such inflammatory conditions can display infiltrates known as lymphoma-like lesions, characterized by mature mantle zones, a lack of atypia, and uniform infiltrate, in contrast to malignancy [3, 13]. BCL-2 immunostaining aids in distinguishing benign from malignant lymphoid proliferation, with BCL-2 being negative in the germinal centers of the former [10]. The Papanicolau test has a low sensitivity for this pathology, and superficial biopsies often yield inconclusive results due to the stromal origin of PFGTL. Thus, deeper or excisional biopsies are recommended for definitive diagnosis [4, 12].

Because most cases are treated preoperatively as other gynecological masses, staging often follows the International Federation of Gynecology and Obstetrics (FIGO) system. Although hematologists traditionally follow the Ann Arbor staging system, gynecologists prefer the FIGO system even after confirming the diagnosis [6]. Prognosis varies with age, staging, and serum lactate dehydrogenase levels [12, 14].

In the largest case series in the literature, 5-year overall survival reached approximately 70%, with cancer-specific survival at around 75%. Follicular lymphoma cases had the best prognosis, while Burkitt's lymphoma showed the poorest survival rates [7]. In a systematic review comprising 34 primary cervical lymphoma cases by Stabile et al., 93.5% of patients were in remission after one year of follow up [9].

Currently, there are no standardized treatment guidelines for PFGTL. However, in most cases, patients undergo debulking surgery followed by chemotherapy after establishing the diagnosis, with or without radiotherapy [3, 6]. Surgical procedures include simple hysterectomy and total abdominal hysterectomy with uni- or bilateral salpingo-oophorectomy [3]. Yet these procedures often serve a diagnostic, rather than a curative role [9]. This is reflected in a study by Nasioudis et al., where nearly 54% of patients received surgical treatment alone [7]. Some recommend radiotherapy as first-line therapy in certain subtypes, resistance to chemotherapy, and massive tumors, highlighting its minimal adverse effects and its role in managing lymphadenopathies [9, 10]. Notably, chemotherapy presents the advantage of preserving ovarian function while addressing micrometastases, making it a preferred option in fertility-sparing approaches [7, 9, 15].

Standard NHL chemotherapy regimens, such as rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP) are widely used as first-line therapy after diagnosis [16].

Signorelli et al. concluded that chemotherapy alone or as neoadjuvant therapy achieved complete remission in 75% of patients [8]. Capsa et al. reported chemotherapy as the primary treatment in 62% of cases [10].

In a series spanning 33 years by Ahmad et al., 5-year survival reached 86%, with the highest survival among

patients receiving combined surgery, radiation, and chemotherapy [12].

Conversely, Nasioudis et al. did not observe survival benefit from combining surgery and radiotherapy compared to either treatment alone [7].

On diagnosis, our patient initiated therapy with CHOP regimen, but her health deteriorated after receiving the second dose, suffering from neutropenic fever and a massive hemorrhage.

In the current report, we describe a case of PFGTL causing bilateral hydronephrosis with subsequent acute kidney injury. To our knowledge, this is the first case in the literature to describe organ failure associated with PFGTL, further highlighting the unpredictable nature of this entity.

To sum up, PFGTL is an exceedingly rare disease, with many cases remaining undiagnosed prior to excision and pathological analysis. Symptoms mimic those of other gynecological tumors.

Although there is no consensus around treatment, chemotherapy is often favoured as a first-line option. Our case stands out among the literature thanks to its aggressive nature, underscoring the heterogenous manifestations of this disease.

Study limitations

Due to the economical situation and difficulty in sourcing the necessary medical equipment in our home country, the immunohistochemical studies performed on our patients were suboptimal.

Abbreviations

AUB	Abnormal uterine bleeding
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone
CT	Computed tomography
DLBCL	Diffuse large B-cell lymphoma
FIGO	International Federation of Gynecology and Obstetrics
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin's lymphoma
PET	Positron emission tomography
PFGTL	Primary female genital tract lymphoma
R-CHOP	Rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone
US	Ultrasound

Acknowledgements

We would like to express my heartfelt gratitude to Dr. Sameh Alramadani (samehalramadani@gmail.com) for his invaluable assistance with the immunohistochemical staining slides.The authors would like to thank Dr. Zabia Alnabelsi for her contribution in collecting data and documents related to the case.

Author contributions

R.AD and R.A were major contributors in article writing and editing various drafts of the manuscript. Y.S and B.M and drafted the paper and critically reviewed the manuscript. A.D was the supervisor. All authors reviewed and approved the final manuscript R.AD is the corresponding author.

Funding

The authors did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not required for case reports at our hospital. Single case reports are exempt from ethical approval in our institution.

Consent for publication

Written informed consent was obtained from the patient's next of kin for publication of this study. A copy of the written consent is available for review by the Editor-in-Chief of the journal on request.

Competing interests

The authors declare no competing interests.

Received: 6 March 2025 / Accepted: 5 May 2025
Published online: 22 May 2025

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