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Case series

Primary gynecological non-Hodgkin's lymphoma: A differential diagnosis of a pelvic mass☆

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ABSTRACT

Primary Non-Hodgkin's lymphoma (NHL) can mimic gynecological malignancy, presenting as a pelvic mass in any organ of the female genital tract. Patients can present with elevated CA-125 and may lack the classical symptoms associated with lymphoma, such as fatigue, fever, night sweats and weight loss. We describe five patients that presented with primary NHL of the genital tract. Patients 1, 2, and 3 were not diagnosed pre-operatively, and underwent unnecessary cytoreductive surgery, while patients 4 and 5 were diagnosed by pre-operative biopsy. The diagnosis of primary pelvic lymphoma should be in the differential diagnosis of gynecological malignancies. Awareness of the disease and pre-operative diagnosis can be beneficial, as the patient may be able to avoid unnecessary staging operations and disease cytoreduction.

1. Introduction

Non-Hodgkin lymphoma (NHL) encompasses a diverse group of neoplasms including B-cell and T-cell lymphomas. NHL is the seventh most common malignancy and the eighth most common cause of cancer death (SEER Database, n.d.). The incidence of this disease has doubled since the 1970s, with the rate of extra-nodal tumors increasing more than nodal tumors (Trenhaile and Killackey, 2001). Although the primary site of origin for lymphomas is the lymph nodes and other lymphoid tissue, approximately 10–35% of patients have primary extranodal lymphoma at the time of diagnosis. Of these cases, less than 1% originate in the female genital tract (Kendrick and Straughn, 2005). Recently, cases of primary pelvic NHL have been reported in the retroperitoneum, ovary, uterine corpus, uterine cervix, vagina and vulva (Trenhaile and Killackey, 2001). Most patients lack the classical "B-cell" symptoms associated with lymphoma, such as fatigue, fever, night sweats and weight loss. We report five cases of extra-nodal NHL of gynecologic origin presenting with varying signs and symptoms, most commonly pelvic mass, and review current management strategies.

2. Case 1

A 67-year-old gravida 4 para 3 female, postmenopausal for 15 years, presented with pelvic pain. The patient denied weight loss, fever, night sweats, fatigue, vaginal bleeding, or abdominal pain. Physical examination revealed a 12 week sized uterus with a palpable 3 × 3 cm mass in the left adnexa. Transvaginal ultrasonography confirmed a hypoechoic solid 3.1 × 2.9 × 1.2 cm mass in the left ovary suspicious for malignancy. Pre-operative CA-125 was 14 U/ml.

The patient underwent a total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and right pelvic lymph node dissection. Intraoperative findings revealed a 10-week size uterus with a 3 cm solid left adnexal mass, with pathology demonstrating a fibroma involving the left ovary. A second large inflammatory appearing mass was also noted near the right common iliac artery. The mass was evaluated by the surgical team intraoperatively and tissue from the surrounding area was biopsied. The biopsy showed reactive lymphoid tissue. Intra-operative surgical impression was consistent with inflammatory changes secondary to an underlying aneurysm.

However, post-operative CT of abdomen and pelvis with contrast showed a right sided 10 × 4.6 × 2.6 cm retroperitoneal abnormal soft tissue mass originating from the mid-abdomen level. It was encasing the right common iliac artery and the external iliac artery. This mass was vascularized and flushed with the anterior surface of the inferior vena cava, however there was no evidence of an aneurysm as initially suspected.

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This mass was biopsied and identified as a monoclonal kappa B-cell population lacking CD5 or CD10 expression. The cells had moderate expression of CD20 and CD18. This was consistent with a marginal zone B-Cell lymphoma or lymphoplasmacytic lymphoma. She received 6 cycles of Rituximab and Bendamustine for indolent type lymphoma. She remains disease free at 28 months follow-up.

3. Case 2

A 51-year-old gravida 2 para 2 female, presented to her gynecologist complaining of pelvic pain and pressure. She reported regular menses every 28 days. Review of systems was negative for fever, chills, dysuria, night sweats, nausea, vomiting, and weight loss. Physical examination revealed a 22-week size uterus without palpable adnexal masses.

Pelvic ultrasound and CT scan demonstrated a leiomyomatous uterus, and also revealed moderate pelvic ascites and a 10.6 × 12.6 × 14.7 cm solid uterine or adnexal mass. Pre-operative labs were normal with the exception of an incidental finding of hypercalcemia (total serum calcium of 12.8 mg/dl) and low hemoglobin (9.1 mg/dl). Her CA-125 was elevated at 352 U/ml.

Intraoperative assessment showed a 12-week size uterus with ovaries that had bilateral masses with the left measuring approximately 15 × 12 cm and the right 15 × 13 cm. They involved the parametrial tissue and were closely associated with the infundibular pelvic ligament. One liter of bloody ascites was evacuated. Frozen section of the mass was inconclusive, with a possible diagnosis of lymphoma or sarcoma. The patient underwent an exploratory laparotomy, radical hysterectomy, tumor debulking, omentectomy, and bilateral pelvic lymph node dissection. She was debulked to zero residual disease.

Postoperatively, the patient was stable. The final pathology report revealed B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma. It involved both adnexa, pelvic peritoneum, and anterior abdominal wall. Immunohistochemical stains revealed B-cells expressing the CD20 marker and, weakly, the CD45 marker.

The patient received six cycles of R-CHOP (Rituximab- Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) and radiation therapy post-operatively. Her disease progressed while on chemotherapy. MRI of the brain revealed CNS involvement. She received 8 courses of 12.5 mg intrathecal methotrexate treatment. Her disease continued to worsen despite therapy. She expired twenty months after her initial diagnosis.

4. Case 3

A 53-year-old gravida 2 para 2 female presented to her primary care physician complaining of malaise, decreased appetite, and unintentional 14 lb weight loss over a period of one month. She also complained of right sided pelvic pain. The patient was status post supracervical hysterectomy nine years prior secondary to uterine fibroids. Her most recent cervical cytology was negative.

CT scan of the abdomen and pelvis with contrast revealed moderate right-sided hydronephrosis secondary to a suspicious 8.3 × 4.6 cm retroperitoneal mass in the right pelvis that was surrounding the distal right ureter. The patient's CA-125 level was 24 U/ml. She underwent a laparoscopic bilateral salpingo-oophorectomy, right pelvic lymph node sampling with multiple intraoperative biopsies.

Post-operative pathology report was consistent with diffuse large B-cell lymphoma involving the right ovary, fallopian tube, and pelvic mass. Immunohistochemical stains revealed sheets of large atypical B-lymphocytes positive for CD10, CD20, and CD45. The atypical lymphocytes were also positive for BCL-6 and MUM-1, supporting the diagnosis of diffuse large B-cell lymphoma, germinal center subtype.

A post-operative PET CT scan showed isolated FDG (Fludeoxyglucose F18) uptake within the deep central/right-sided pelvic soft tissue, corresponding to the known area of neoplasm. Bone marrow biopsy was negative for lymphoma involvement. The patient received treatment with six cycles of R-CHOP followed by radiation therapy for Stage IE bulky disease. Repeat PET CT scan after adjuvant therapy showed complete remission.

5. Case 4

A 44-year-old gravida 1 para 1 female presented to the emergency room complaining of pelvic pain and left leg pain that necessitated her to ambulate with the assistance of a cane. She reported a 20–25 lb weight loss over the previous five months. The patient was cachectic and in acute distress. Physical exam revealed an enlarged uterus and a fixed pelvic mass. Her CA-125 level was elevated at 381 U/ml.

Pelvic ultrasound showed a 17 × 10 × 11 cm heterogeneous hypoechoic pelvic mass that displaced the uterus anteriorly. The uterus was enlarged, extending to the mid-abdomen, and the ovary could not be visualized. Severe right hydronephrosis was noted.

Examination under anesthesia confirmed the imaging findings. The mass was fixed to the left pelvic sidewall as well as to the anterior uterus and cervix. The cervical canal was severely stenotic and could not be entered. A biopsy of the cervix and a needle biopsy of the mass were performed. Pathology of the cervix revealed atypical lymphoid infiltrate favoring a Diffuse Large B-cell Lymphoma of non-germinal center type.

The patient was referred to hematology/oncology for further follow up. She was started on chemotherapy with R-CHOP. Although after two months PET CT scan showed interval resolution of the pelvic mass, the patient started complaining of dizziness and blurred vision. Brain MRI at this time showed increased signal on T2 weighted imaging with associated enhancement of the mid brain and thalamus. These findings were consistent with lymphoma involvement in the brain. She was referred to a tertiary cancer center for further care.

6. Case 5

A 43 year old gravida 1 para 1 was referred from her primary care physician with menorrhagia and a vaginal mass found on examination. The patient felt well and had no other complaints. She reported regular menstrual cycles every 28–30 days. Pap smear done one year previously was negative for any abnormalities. She had no significant medical or surgical history. Physical examination revealed a fixed 7 × 8 cm mass in the rectovaginal septum that was either originating from the rectum or the cervix. The mass extended to the left pelvic sidewall.

Pelvic ultrasound and MRI confirmed a 6.5 × 8.6 × 8.4 cm solid mass arising from the cervix. A needle biopsy of the posterior vaginal mucosa overlying the mass revealed diffuse atypical lymphoid infiltrates with marked pleomorphism. Immunohistochemical for CD20, CD10, and Bcl2 were diffusely positive. Staining was also positive for BCL-6 and MUM-1 with high proliferation index for Ki-67, supporting the diagnosis of diffuse large B-cell lymphoma, germinal center subtype. The patient received 6 cycles of R-CHOP. Interval PET-CT scan at 6 months follow up showed complete regression of disease.

7. Discussion

Primary gynecologic Non-Hodgkin lymphoma is extremely rare and sporadically reported in the literature. Diffuse Large B-cell lymphomas (DLBCL), comprising approximately 25% of reported NHL cases in the Western world, is the most common lymphoma of the genital tract (Armitage and Weisenburger, 1998). This is evident in our case series, as it was seen in 3 of our patients. In general, B-cell lymphomas have a better prognosis and overall response to traditional treatment than T-cell lymphomas (Ahmad et al., 2014).

The clinical workup leading to an appropriate diagnosis is extremely challenging given the varied clinical presentations as well as laboratory findings of this disease. Some patients with primary gynecological Non-Hodgkin lymphoma present with nonspecific abdominal complaints

such as pain and pressure. Others present with vaginal bleeding and/or discharge. Some are completely asymptomatic with an incidental finding of a pelvic mass. Very few patients have the traditional "B" symptoms associated with lymphomas. Laboratory findings such as elevations in tumor marker CA-125, a marker with limited specificity but nonetheless remaining a predictor of primary ovarian malignancy, can also be seen in primary gynecologic NHL. This, as seen in Cases 2 and 4, make the diagnosis of pelvic NHL even more difficult. In our case series, 2 patients out of the 5 reported weight loss and only one experienced malaise. In a recent study of 36 patients with Non-Hodgkin's lymphoma originating in gynecological organs, only 17% patients have such constitutional symptoms (Ahmad et al., 2014). The most common presentation in this large review was vaginal bleeding and enlarging pelvic mass (Ahmad et al., 2014). Our series resulted in a similar conclusion, with pelvic mass, vaginal bleeding and pelvic pain as the most common findings.

Once an incisional or excisional biopsy has been done and a tissue diagnosis of Non-Hodgkin lymphoma has been confirmed, a complete staging workup must be initiated (Chen et al., 2015). This should include a full body CT and/or PET scan followed by a bone marrow biopsy (Kendrick and Straughn, 2005). PET scan is now commonly being used in staging, detecting recurrence, and monitoring treatment (Chen et al., 2015). Other markers such as CA-125 levels, as mentioned above, can also be useful. Elevated CA-125 (concentrations above 35 U/ml) at the time of diagnosis of NHL has been associated with a decreased 5-year survival rate (Allen et al., 2004). In a study by Bairey et al., serum CA-125 levels were prospectively measured in 108 consecutive patients with NHL. Of these patients, 43% had elevated CA-125 (Bairey et al., 2003). Higher levels of CA-125 were associated with advanced disease stage, extranodal disease, bulky tumors, occurrence of B symptoms, pleural and peritoneal effusions, involvement of bone marrow, high serum LDH levels, high serum beta2 microglobulin and poor performance and response to treatment. This was evident in our case series, as the two patients with the highest levels of CA-125 (Cases 2 and 4) both had CNS involvement and poorer outcome.

NHL tumor cells are diagnosed based on their morphology and immunotyping. These tumors have an extremely heterogeneous presentation, even from a pathologic standpoint (Menon et al., 2012). Some distinction can be made in rate of growth, which can alter the course of treatment of these conditions. Diffuse large B-cell lymphoma and Burkitt's lymphomas are rapidly proliferative forms of lymphomas. Other sub-types, such as follicular lymphomas, marginal zone lymphomas and lymphoplasmacytic lymphomas, have a more indolent course.

Rapidly proliferative NHL tumors are highly responsive to chemotherapy (Menon et al., 2012). Current first-line therapy is the standard chemotherapy of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) combined with Rituximab for at least 3 cycles and 6 for bulky disease. This chemotherapy regimen, when combined with radiation therapy, yields a cure rate of ~60–70% (Cohn et al., 2007). R-CHOP is associated with a wide range of adverse effects such as cardiac, hematologic and neurologic toxicities (Rummel et al., 2013). More indolent lymphomas, which have a slower growth pattern, do not require an aggressive treatment such as R-CHOP. In patients with indolent NHL or mantle-cell lymphoma, Bendamustine-Rituximab treatment prolonged progression-free survival of patients, increased complete response rate and decreased toxicity when compared to R-CHOP (Rummel et al., 2013). The patient in Case 1 had an indolent type lymphoma and therefore underwent chemotherapy with B-R regimen, whereas patients 2, 3, 4, and 5 required treatment with R-CHOP.

Diagnosis of pelvic NHL can be difficult, as this disease can mimic gynecologic malignancies such as endometrial cancer, cervical cancer, sarcoma or ovarian cancer depending on disease site. Furthermore, pre-operative diagnostic imaging and intraoperative frozen section are not always conclusive. This uncertainty can result in a patient undergoing unnecessary tumor debulking. In our case series, if a diagnosis of NHL were known pre-operatively, patients 1, 2 and 3 could have avoided surgery and been treated conservatively. Surgical staging and cytoreduction are not indicated in patients with diagnoses of pelvic NHL, as these patients are very responsive to chemotherapy. Biopsies of suspicious lesions pre-operatively can help make a diagnosis, as seen in patients 4 and 5 in our case series.

In patients presenting with a pelvic mass, placing lymphoma on the list of differential diagnoses requires a very high index of suspicion and selection of which patients to biopsy can be challenging. From our experience, a diffuse retroperitoneal soft tissue mass encasing several soft tissue or vascular structures could possibly be a lymphoma. This was the presentation in Cases 1, 2, and 4. Vaginal lymphoma can also have a diffuse distribution in the pelvis. The patient in Case 5 had vaginal mass that involved the recto-vaginal septum as well as several other pelvic organs. This presentation is consistent with a series reporting sixteen cases of NHL involving the vagina (Vang et al., 2001). In this series, the most common finding detected by pelvic examination was a vaginal mass with a bulky pelvic distribution, including multiple other contiguous non-vaginal structures (Vang et al., 2001). In this series, 13 of the patients also had vaginal bleeding as a complaint.

Ovarian lymphomas are the most difficult to suspect pre-operatively as clinical findings are very similar to epithelial ovarian malignancy. The age of presentation of ovarian NHL is variable, ranging from 21 to 69 years in one large series of 30 cases (Vang et al., 2001). Bilateral masses, similar to the patient in Case 3, have been reported in 41–71% of patients with ovarian lymphoma (Trenhaile and Killackey, 2001). Due to lack of any definitive features suggesting lymphoma, we believe that adnexal masses presenting with an elevated CA-125 or ascites should be treated like primary gynecological ovarian malignancy and explored surgically. Fine needle biopsy of these masses could result in tumor dissemination if it is indeed a gynecological ovarian malignancy.

8. Conclusion

With the absence of B-Cell symptoms, findings of abnormal vaginal bleeding, pelvic pain, elevated CA-125 and pelvic mass may be highly suggestive of a gynecologic malignancy. However, it is important to include NHL in the differential diagnosis of pelvic masses. Awareness of the disease and pre-operative diagnosis can be beneficial, as the patient may be able to avoid unnecessary staging operations and disease cytoreduction.

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