Two Cases of Non-Hodgkin’s Lymphoma Involving the Uterus

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Abstract

Diagnosis of uterine lymphoma is challenging due to its rarity and non-specific presentation. Treatment is also difficult since there is no standard treatment. We report our experience with two cases of lymphoma involving the uterus. The first patient was a 66-year-old with chief complaint of lower abdominal pain. She was diagnosed as lymphoma of the uterus by laparotomy. Chemotherapy failed and she died in the course of a year. The second patient was a 63-year-old who presented with general fatigue. Tissue biopsy and CT scan revealed lymphoma of the stomach with multiple metastases including the uterus. She was treated with chemotherapy followed by radiation therapy, but died 18 months later. Lymphoma involving the uterus is rare and diagnosis can be difficult. Clinicians should be aware of this rare disease for prompt diagnosis. Treatment should be individualized according to the condition of each patient.

Keywords: Non-Hodgkin's lymphoma; Extranodal lymphoma; Uterine lymphoma; Uterine neoplasm; Combination therapy

Introduction

Non-Hodgkin's Lymphoma (NHL) can originate from sites other than the lymph node. Among those extranodal sites, uterus is a rare site of involvement [1]. Moreover, the presentation of uterine lymphoma lacks any specific symptoms [2], thus it is difficult to distinguish it from more common uterine neoplasms such as uterine fibroids or sarcoma. As a result, diagnosis can be delayed, possibly leading to poor prognosis. Once the diagnosis is made, treatment poses another difficulty. The nature of the low incidence of the disease makes randomized trials difficult, so there are no standards for treatment. Taking account of the studies done on treatment of extranodal lymphomas in general, it seems localized treatment with radiation therapy or surgery combined with chemotherapy improves outcome [3,4].

We report our experience with two cases of lymphoma NHL both of which were first noted by enlargement of the uterus.

Cases

The first case was a 66-year-old who presented with three weeks of lower abdominal pain. She was transferred to our hospital from a local clinic because of bilateral hydronephrosis and enlargement of the uterus. Clinical examination was insignificant other than an enlarged uterine mass of 11.6×10.1×10.0 cm on transvaginal ultrasound. There were no signs of peripheral lymphadenopathy. Both cervical and endometrial smears were negative. Tumor markers CA125, CA19-9, AFP, CEA and SCC were not elevated. Lactate Dehydrogenase (LDH) was mildly elevated (448 U/l). CT and MRI revealed a diffuse enlargement of the uterus extending to the colon, bladder and the retroperitonium (Figure 1). No enlargement of abdominal lymph nodes was observed. She underwent emergent nephrostomy because of rapid renal failure due to worsening hydronephrosis. By then, the uterine mass had grown to 18.6×16.2×14.1 cm. Laparotomy and colostomy was performed under the condition of her chronic hepatitis B status. Rituximab was not omitted with the informed consent of the patient. HBV DNA level remained unchanged during chemotherapy. After seven courses of chemotherapy, there was significant decrease in the size of the tumor confirmed by CT scan, and blood LDH level decreased to normal. However, the lymphoma metastasized to the left inguinal lymph node. She then went through R-DeVIC (rituximab, carboplatin, etoposide, ifosfamide and dexamethasone) as second line chemotherapy, but it was unable to control the disease. Radiation therapy was started. After two weeks, febrile neutropenia occurred and this led to sepsis. Her condition deteriorated rapidly and died. Her death was approximately one year after initial diagnosis.

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The second case was a 63-year-old complaining of general fatigue and loss of appetite which began three months ago. She was referred to our hospital suspected of massive leiomyoma of the uterus. Clinical examination revealed an enlarged pelvic mass reaching up to the navel. There was no sign of peripheral lymphadenopathy. Tumor marker CA125 was elevated (315.4U/ml). CA19-9 and CEA was not elevated. LDH level was 732U/l. Result of systematic workup; she had thickening of stomach wall, abdominal lymphadenopathy, and left pleural effusion (Figure 3). She was immediately admitted to our hospital due to low SpO2. Pleural tap was performed but there was no evidence of malignancy in the effusion. Our temporal diagnosis was stomach cancer and uterine metastasis. She went through tissue biopsy of the stomach and endometrium. Immunohistopathology of both endometrium and stomach was negative for CD3 and UCHL-1, and positive for CD20 and CD79a (Figure 4). Diagnosis of DLBCL primary involving the stomach was made. She was treated with eight courses of R-CHOP and achieved PR. Level of LDH normalized, there were no signs of pleural effusion or ascites, and all the involved sites responded to treatment significantly. During a watch and wait period, the patient experienced left facial nerve paralysis. Multiple lesions of brain and spine were confirmed by MRI. Total brain and spine radiation was started, but it was unable to control the disease. The patient died 18 months after initial diagnosis.

Discussion

Uterus is not a common site of involvement in NHL. Freeman et al. analyzed data from The Cancer Registries of the End Results Group, which consists of data from over 100 hospitals in the United States and reported that of the 1467 cases of extranodal NHL, only six cases (0.5%) were uterine in origin [1]. Common sites for extranodal lymphoma include skin and the gastrointestinal tract. Until present, there have been a considerable number of case reports describing uterine involved NHL. A Medline search resulted in nine case reports describing total of 10 cases of primary uterine lymphoma within the past 5 years [5-13]. A summary is shown in Table 1. The median age at presentation was 54.5 years (range 36-85). The most frequent complaint was

<table>
<thead>
<tr>
<th>Age</th>
<th>Chief complaint</th>
<th>Ann Arbor Stage</th>
<th>Histology</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 77</td>
<td>Uterine prolapse</td>
<td>IAE</td>
<td>MZL</td>
<td>Vaginal hysterectomy</td>
<td>CR</td>
</tr>
<tr>
<td>2 47</td>
<td>Brown discharge</td>
<td>IIIEB</td>
<td>DLBCL</td>
<td>R-CHOP</td>
<td>CR</td>
</tr>
<tr>
<td>3 72</td>
<td>Abdominal fullness</td>
<td>IV</td>
<td>DLBCL</td>
<td>TC, TAH, R-THP-COP</td>
<td>CR for 3 years</td>
</tr>
<tr>
<td>4 85</td>
<td>Postmenopausal bleeding</td>
<td>IE</td>
<td>DLBCL</td>
<td>R-CHOP</td>
<td>CR</td>
</tr>
<tr>
<td>5 48</td>
<td>Irregular bleeding</td>
<td>not stated</td>
<td>NK Cell</td>
<td>Chemotherapy not specified</td>
<td>CR</td>
</tr>
<tr>
<td>6 36</td>
<td>Intermittent bleeding</td>
<td>IB</td>
<td>NK Cell</td>
<td>CHOP</td>
<td>CR</td>
</tr>
<tr>
<td>7 49</td>
<td>Abdominal fullness</td>
<td>IIA</td>
<td>DLBCL</td>
<td>R-CHOP, Radiation</td>
<td>CR for 20 months</td>
</tr>
<tr>
<td>51</td>
<td>Abdominal pain</td>
<td>IIEA</td>
<td>DLBCL</td>
<td>R-CHOP, Radiation</td>
<td>CR for 19 months</td>
</tr>
<tr>
<td>8 79</td>
<td>Urinary obstruction</td>
<td>not stated</td>
<td>DLBCL</td>
<td>R-CHOP</td>
<td>CR for 19 months</td>
</tr>
<tr>
<td>9 58</td>
<td>Abdominal mass</td>
<td>not stated</td>
<td>Burkitt</td>
<td>TAH, BSO, Appendectomy, PALD, PLD, Chemotherapy*</td>
<td>CR for 9 months</td>
</tr>
</tbody>
</table>

*Vincristine, rituximab, high-dose methotrexate with leucovorin/rescue, and intrathecal methotrexate

BSO: Bilateral Salpingo-oophrectomy; CR: Complete Remission; DLBCL: Diffuse Large B Cell Lymphoma; NK: Natural Killer; PALD: Para-Aortic Lymph Node Dissection; PLD: Pelvic Lymph Node Dissection; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-THP-COP: Rituximab, pirarubicin, cyclophosphamide, vincristine and prednisone; TAH: Total Abdominal Hysterectomy; TC: Paclitaxel and Carboplatin

Table 1: Case reports of primary uterine lymphoma published in the past five years. The numbers 1-9 correspond to reference number 5-13 in that order.

Figure 3: T2WI of the uterus in sagittal section showing diffuse enlargement of the uterus. Signal intensity is relatively homogeneous.

Figure 2: The tumor was composed of large lymphoid cells positive for CD20. (Original magnitude×40).

Figure 4: Endometrial biopsy specimen showing large lymphoid cells positive for CD20. (Original magnitude×40).
vaginal bleeding/discharge. In some of the reports, Ann Arbor stage was not specified, but most of the cases were early stage tumors. Most common histological type was DLBCL. They were treated with various combinations of surgery, chemotherapy and radiation therapy. These findings were consistent with other case reports with literature review [2,3,11,14].

Primary uterine lymphoma is defined as (1) disease clinically confined to the uterus at initial time of diagnosis, (2) absence of leukemia, and (3) at least several months’ interval between the appearance of secondary site and the primary site. When the stage is advanced, it is difficult to know whether the site of involvement was primary or secondary. Naturally, most of primary uterine NHL reports are of Ann Arbor stage IE or IIE. The strength of our report is that surgery was performed, which made accurate staging of advanced stage primary NHL. On the other hand, biopsy was not performed on the patient prior to laparotomy since NHL was not on our differential diagnosis. Retrospectively, biopsy could have avoided the patient's risk of surgery. In a case report of six primary cervical lymphoma, Chan et al. reported that three patients were diagnosed as lymphoma based on cervical biopsy. Two patients had a negative biopsy, and one patient's biopsy result was poorly differentiated carcinoma. Of the two patients with negative cervical biopsy, one underwent CT-guided biopsy. For the other biopsy-negative patient and the false biopsy result patient, surgery revealed the final diagnosis [14].

Our first case was found to be a Hepatitis B Virus (HBV) carrier on routine preoperative blood exam. It is reported that HBV carriers can experience reactivation of the virus after chemotherapy. Entecavir prophylaxis is now available to prevent flair-up in these patients. However, it is still not clear whether patients with low viral load, as in the case reported here, should routinely receive antiviral prophylaxis. Huang et al. reported in their randomized control trial of 80 patients that patients with undetectable viral load can experience reactivation, and entecavir prophylaxis can prevent rituximab associated HBV reactivation [15].

Among extranodal sites of NHL, uterine lymphoma is unique in that surgery becomes an option of treatment if the disease is localized [3]. Moreover, it is not unusual to reach diagnosis after surgery as in the first case we described since preoperative diagnosis is sometimes difficult [14]. Miller et al. compared chemotherapy plus radiation therapy for localized intermediate and high-grade NHL and concluded that combination therapy improves outcome [4]. In conclusion, since presentation of uterine lymphoma is heterogeneous, treatment plans should be made individually according to the situation in which the diagnosis is established. If the disease is localized, chemotherapy plus radiation therapy appears to be effective.

Conclusion

In order to facilitate diagnosis and treatment of uterine lymphoma, physicians should keep in mind that the presentation is non-specific. Clinicians should have this rare disease on their differential diagnosis as a cause of uterine neoplasm. Treatment must be individualized depending on the extent to which the disease is spread and the conditions it has caused.

References