CASE COMMENTARY

Primary non-Hodgkin's Lymphoma of the Uterine Cervix

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Abstract

Primary malignant lymphoma of the cervix is a rare disease. Because the number of reports of this cancer is limited, there is no consensus on its management, prognosis or the efficacy of various treatments. Primary malignant lymphoma of the cervix stage Ib was diagnosed in a 25-year-old woman. The patient was treated with 6 courses of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Clinical and pathological responses were complete. This case supports current thinking in that, in selected young patients with primary malignant lymphoma of the cervix who desire to preserve fertility and ovarian functions, combination chemotherapy regimens such as CHOP are the treatment of choice.

Key Words: Non-Hodgkin's lymphoma - uterine cervix - chemotherapy

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Background

Primary malignant lymphoma of the female genital tract, a rare form of extranodal non-Hodgkin's lymphoma (NHL), can occur in the ovary, uterine corpus, cervix, vagina, and vulva. The ovary is the most frequent site for NHL involvement of the gynecological tract (Vang et al., 2001). Primary malignant lymphoma of the cervix is a rare disease.

The incidence is unknown. In 1974, Chorlton et al. reported the occurrence of primary cervical lymphoma in only 6 out of 9500 (0.06%) lymphomas in females (Chorlton et al., 1974). Because the number of reports of primary malignant lymphoma of the cervix is limited, there is no consensus on its management, prognosis or the efficacy of various treatments. A review of the limited literature indicates that radical surgery, radiotherapy, chemotherapy, or combinations of these have been tried (Komaki t al., 1984; Muntz et al., 1991; Yokoyama et al., 2001; Szantho et al., 2003; Dursun et al., 2005; Semczuk et al., 2006). In this report we describe a rare case of primary NHL of the cervix which then had complete remission after receiving chemotherapy.

Clinical Presentation

A 25-year-old woman, was referred to Songklanagarind Hospital, with a 2-week history of postcoital bleeding and increasing vaginal discharge. The patient underwent a cervical biopsy due to an abnormal lesion at the lower portion of the uterine cervix. The pathology was consistent with a malignant lymphoma, diffuse large B-cell type, with strong positive immuno-histochemical staining to CD20 and leukocyte common antigen (LCA) (Figure 1), and negative for CD3 and cytokeratin.

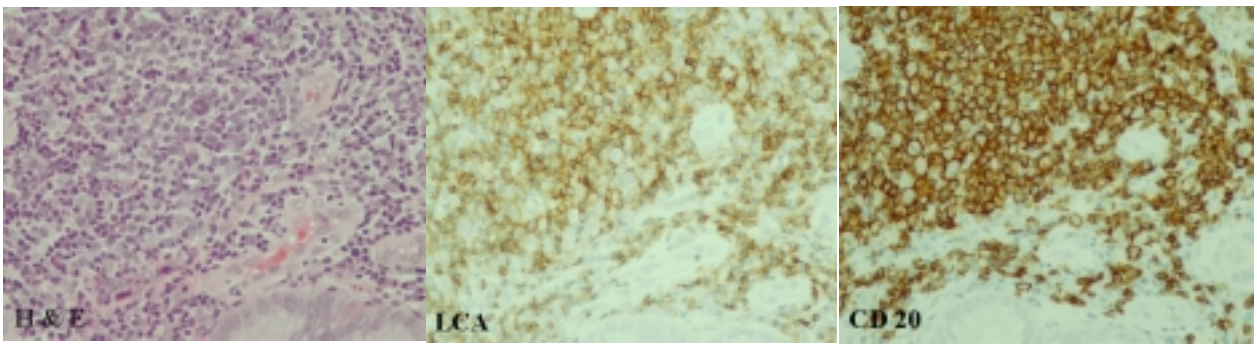

Figure 1. Diffuse Infiltration of Cervical Stroma by Lymphoma cells with Prominent Vasculature (a). Tumor Cells Strongly Express Leukocyte Common Antigen (LCA) (b) and CD20 (c). Semi-serial Sections

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The review of systems was negative for history of prolonged fever, weight loss or night sweats. Previous annual cervical cytology exams had been normal. There was no peripheral lymphadenopathy and examination of the abdomen was unremarkable. The remaining results of the physical examination were within normal limits. The pelvic examination revealed a large (4 cm x 4.5 cm) cervical ectropion with contact bleeding. The uterine body and both adnexa were normal in size and both parametria were free. A colposcopic examination revealed an extended transformation zone without abnormal findings (Figure 4a). A lumbar puncture did not show malignant cells. Clinical staging work ups such as chest radiograph and intravenous pyelography were normal.

Computed tomography (CT) of the abdomen and pelvis showed a large enhancing cervical mass, 57x31x49 mm, connecting with the endometrial cavity and suspected extension to the bilateral parametrium, no gross adenopathy. She was HIV-negative, and other blood tests were normal. She was given the diagnosis of stage Ib cervical cancer according to the International Federation of Gynecology and Obstetrics classification (FIGO), and IE according to the Ann Arbor classification. The patient was treated with 6 courses of CHOP on a monthly basis. After 3 courses of chemotherapy, a CT scan revealed almost complete resolution of her disease, and after the completion of the 6 courses, her colposcopic examination and a blind biopsy of the cervix were normal. As of writing, the patient remains without evidence of disease 29 months after completion of treatment (36 months after initial diagnosis). No remarkable side effects were observed during treatment.

Discussion

Primary cervical lymphoma is rare. It is accepted that the diagnosis of primary lymphoma of the cervix must fulfill the criteria proposed by Fox and More (1965). The case at hand fulfilled these criteria, which included a lesion confined to the cervix on diagnosis, and no evidence of lymphoma in other organs for at least several months during follow up (Fox and More, 1965; Semczuk et al., 2006).

Non-Hodgkin's lymphomas (NHL), especially extranodal NHL, are increasing in incidence, but the etiology of much of this increase is still unclear. Trenhaile and Killackey have postulated that the etiology of the increase includes infectious agents such as the human immunodeficiency virus (HIV), immunosuppressive therapies, environmental exposure to pesticides and pollutants, and improved diagnostic techniques (Trenhaile and Killackey, 2001). Although some authors have suggested a possibility that Epstein-Barr virus or human papilloma virus may play a role in the etiology of gynecologic NHL, there has been to date no reliable evidence on the role of these viruses in the development of cervical lymphoma (Gutman et al., 1998; Yang et al., 1998;Vang et al., 2001). Other previous studies have suggested a link between chronic inflammation and the development of stomach and breast lymphomas (Aozasa et al., 1992; Hussell et al., 1993). The possible association of chronic inflammation and cervical lymphoma has been addressed by Aozasa et al., in a study in which they found formation of lymph follicles in one of four such cases of cervical lymphoma, suggesting the presence of preceding inflammation in the cervix (Aozasa et al., 1993).

The age at diagnosis in the known cases has ranged from 20 to 80 years, with the median age in the studies varying from 40 to 52 years (Komaki et al., 1984; Muntz et al., 1991; Chan et al., 2005; Dursun et al., 2005; Cantu de Leon et al., 2006). Presenting symptoms mentioned in previous reports are vaginal bleeding, vaginal discharge, pelvic pain, dysparuenia, and B symptoms (Yokoyama et al., 2001; Szantho et al., 2003; Chan et al., 2005; Dursun et al., 2005; Heredia et al., 2005; Cantu de Leon et al., 2006; Semczuk et al., 2006). The most common complaint is abnormal vaginal bleeding (Chan et al., 2005; Dursun et al., 2005; Cantu de Leon et al., 2006). Although B symptoms, which include fever, weight loss, night sweats, and fatigue, are often associated with systemic lymphoma, they are uncommon in cervical lymphoma (Dursun et al., 2005). Our case presented with abnormal vaginal bleeding and vaginal discharge without B symptoms. It is also of interest to note that approximately 10-20% of patients to date reported have been asymptomatic and the cervical lymphoma was only discovered on routine physical examination or as an incidental finding at the time of a hysterectomy for other indications (Muntz et al., 1991; Dursun et al., 2005).

Cervical lymphomas generally manifest as a rapid endophytic pattern of growth, and half of all reported cases have exceeded 4 cm in diameter at diagnosis (Muntz et al., 1991), as seen in our case. On pelvic examination, gross findings of this cancer may vary from a grossly unremarkable, bulky cervical or pelvic mass to vaginal or parametrial involvement (Yokoyama et al., 2001; Szantho et al., 2003; Chan et al., 2005; Dursun et al., 2005; Heredia et al., 2005; Cantu de Leon et al., 2006; Semczuk et al., 2006; Cohn et al., 2007). In the colposcopic examination, Cantu de Leon et al. suggested that the most important finding is cervical enlargement with or without erosion; a polypoid mass may be found, or a barrel-shaped diffuse enlargement of the cervix as in this case (Cantu de Leon et al., 2006). According to Harris and Scully, up to 67% of these tumors present with a subepithelial mass without obvious ulceration or epithelial abnormality (Harris and Scully, 1984). Therefore, a Papanicolou (Pap) smear might not be useful for diagnosis. In 2005, a large case series found that only 50% of cervical lymphomas had an abnormal Pap smear (Chan et al., 2005). Deep biopsy of the lesion(s) is necessary for diagnosis of this malignant. NHL of the cervix, as it is often misdiagnosed as chronic cervicitis, poorly differentiated carcinoma, sarcoma, or lymphoma-like lesion (Komaki et al., 1984; Vang et al., 2001; Dursun et al., 2005; Chan et al., 2005; Cantu de Leon et al., 2006; Cohn et al., 2007). Immunohistochemical strains are invaluable in aiding in the distinction of many of these entities. In our case, the tumor stained positive for CD20 and leukocyte common antigen (LCA), and negative for CD3 and cytokeratin.

There is no consensus for staging of lymphoma of the cervix, and both the FIGO and the Ann Arbor staging

systems for extra nodal lymphoma are used (Korcum et al., 2007). Imaging such as computed tomography or magnetic resonance imaging is useful in diagnosis, staging and planning of treatment (Komaki et al., 1984; Muntz et al., 1991; Garavaglia et al., 2005; Heredia et al., 2005; Cohn et al., 2007; Korcum et al., 2007).

Treatment regimens reported in the literature have included surgery alone (Chorlton et al., 1974; Chan et al., 2005), radiation alone (Komaki et al., 1984; Muntz et al., 1991), chemotherapy alone (Dursun et al., 2005; Garavaglia et al., 2005; Wannesson L, 2006), and a combination of two or three of these modalities (Stroh et al., 1995; Yokoyama et al., 2001; Szantho et al., 2003; Dursun et al., 2005; Garavaglia et al., 2005; Heredia et al., 2005; Cantu de Leon et al., 2006; Cohn et al., 2007). In at least one study, surgery alone was reported to be useful in curing localized lymphoma of cervix (Chorlton et al., 1974), although other studies have found surgery less useful. Chan et al. reported that one of 6 cases of cervical lymphomas who had a previous subtotal hysterectomy for leiomyoma subsequently underwent trachelectomy with pelvic node dissection, and three months after primary surgery for her lymphoma, she experienced an intra-abdominal recurrence (Chan et al., 2005). Perren et al. also suggested that radical surgery offered no advantage in such cases on the basis of reviewed literature (Perren et al., 1992). In other earlier reports, due to a high response rate and low morbidity, radiation treatment was used as the first line of treatment for stage IE disease (Komaki et al., 1984; Muntz et al., 1991). One notable disadvantage of radiation treatment alone or surgical treatment alone are their inability to treat occult disseminated disease. For young patients with cervical lymphoma who desire fertility preservation, these treatments can compromise fertility and/or ovarian function (Muntz et al., 1991). Although recent studies have proposed that management with a combination of chemotherapy followed by pelvic radiation is apparently the best option with better survival and a 5-year survival rate of up to 100% in some series of primary NHL of the cervix (Perren et al., 1992; Stroh et al., 1995; Vang et al., 2001; Cohn et al., 2007), in this case we chose 6 courses of CHOP for treatment as the patient strongly desired to preserve her ovarian and fertility functions.

CHOP is a first generation combination chemotherapy regimen that has proved equally effective, yet less toxic, than second and third generation regimens for advanced stages of intermediate and high grade NHL (Garavaglia et al., 2005; Korcum et al., 2007). Dursun et al. used 6 courses of CHOP to treat NHL of cervix stage IE, and at the report the patient had remained free of disease for 22 months from the initial diagnosis (Dursun et al., 2005). Sandvei et al. reported a successful pregnancy following treatment of primary lymphoma of the cervix with 6 courses of CHOP, as used in our case (Sandvei et al., 1990). Rituximab is a monoclonal antibody directed against the CD-20 antigen, which is frequently present in lymphoma cells (Evans and Hancock, 2003; Korcum et al., 2007). Recent evidence has suggested that combining rituximab with CHOP gives an improved response rate compared to CHOP alone, showing a synergistic activity (Evans and Hancock, 2003). There is less known about cervical lymphoma and the effectiveness of rituximab treatment. Cohn et al. published 2 case of cervical lymphoma and 1 case of vaginal lymphoma treated with a combination of rituximab with CHOP (Cohn et al., 2007). Survival rates have improved with the addition of rituximab to CHOP in cervical lymphoma, and tests are ongoing.

The prognosis of cervical lymphoma seems to correlate with the stage and grade of the disease (Harris and Scully, 1984; Heredia et al., 2005; Korcum et al., 2007). However, Stroh et al. developed an the International Index score consisting of age of the patient, Ann Arbor stage, number of extranodal sites, performance status, and serum lactic dehydrogenase values, which could be used to predict the outcome for uterine and cervical lymphomas (Stroh et al., 1995).

In conclusion, our case supports current thinking in that, in selected young patients who desire to preserve fertility and ovarian functions, combination chemotherapy regimens such as CHOP are the treatment of choice for primary NHL of the cervix.

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