Malignant lymphoma of the vagina successfully treated with rituximab, adryamicin, cyclophosphamide, vincristine sulfate, and prednisolone

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Summary

Purpose: Primary malignant lymphoma of the vagina is extremely rare. The most common histologic subtype is diffuse large B-cell lymphoma (DLBCL). We report a case of vaginal DLBCL successfully treated with chemotherapy consisting of rituximab, adryamicin, cyclophosphamide, vincristine sulfate, and prednisolone (R-CHOP), followed by pelvic irradiation. *Case:* A 44-year-old Japanese woman was admitted complaining of atypical genital bleeding and puruloid vaginal discharge. Gynecological examination showed an ulceration of the vaginal wall and a hard mass the size of a goose egg beneath the left vaginal wall, which had infiltrated to the left pelvic wall. The pathological diagnosis based on a punch biopsy taken from the vaginal tumor was non-Hodgkin's lymphoma. Based on immunohistochemical study, the tumor was subclassified as activated B-cell type DLBCL. The patient was diagnosed with Ann Arbor Stage IEA DLBCL and Stage III vaginal cancer, according to the International Federation of Gynecologists and Obstetricians (FIGO) classification system. She was successfully treated by six courses of R-CHOP, followed by radiation therapy. The patient is well without evidence of disease 13 months following the initial treatment. *Conclusion:* Little attention has been paid to the use of rituximab in addition to conventional chemotherapy and the importance of clinical and morphological subgrouping of DLBCL arising in the vagina. The present case indicates that the effects of rituximab on the prognosis of vaginal DLBCL must be evaluated, and that clinical use of immunophenotypic subgrouping should be considered for vaginal DLBCL.

Key words: Malignant lymphoma; Vagina; Chemotherapy; Radiation.

Introduction

Secondary involvement of the female genital organs can be seen in up to 40% of disseminated malignant lymphomas, but primary malignant lymphoma of the vagina is extremely rare [1-3]. Chorlton *et al*. [1] reviewed 9,500 cases of lymphomas in women and found only four cases of primary vaginal malignant lymphomas, i.e., an incidence of one in 2,375 cases.

Clinical symptoms of vaginal malignant lymphomas usually include vaginal bleeding (70%), perineal discomfort (40%), and persistent vaginal discharge (20%). However, patients with vaginal malignant lymphoma may also present with a clinically detectable vaginal or pelvic mass [3], or with symptoms of abdominal pain, introital mass, dyspareunia, or urinary frequency [2, 3] and 20% of cases apparently remain asymptomatic [1]. Vaginal malignant lymphomas produce an ill-defined, very firm thickening or induration of the vaginal wall and extend toward the rectum, bladder, or pelvic walls [1-3]. At presentation, contiguous structures and/or regional lymph nodes are commonly involved [3].

Most are non-Hodgkin's lymphomas (NHL). The most common histologic subtype is diffuse large B-cell lymphoma (DLBCL) with immunochemistry staining positive for CD20 [3, 4-8]. Guarini *et al*. [4] reported that 52.9% of cases of vaginal NHL were classified as high-grade and that 90.9% of cases were diagnosed as in Stages IE and IIE. However, in many reports older lymphoma classifications were used and immunophenotypic data were not provided.

In this case report, we present an additional case of vaginal DLBCL successfully treated with chemotherapy consisting of rituximab, adryamicin, cyclophosphamide, vincristine sulfate, and prednisolone (R-CHOP), followed by pelvic irradiation. We also discuss the importance of subclassification of vaginal DLBCL with immunohistochemistry.

Case Report

A 44-year-old Japanese woman (gravida 2, para 2) was admitted complaining of atypical genital bleeding and puruloid vaginal discharge. The patient did not have fever, weight loss, or night sweats. Gynecological examination showed an ulceration of the vaginal wall and a hard mass the size of a goose egg beneath the left vaginal wall, which had infiltrated to the left pelvic wall. Cytology of the cervix, endometrium, and ulcerated vaginal wall were negative. Bilateral inguinal and femoral lymph nodes were not evident. The pathological diagnosis of a punch biopsy taken from the vaginal tumor was NHL (Figure 1). As shown in Table 1, immunohistochemical study subclassified the tumor cells as activated B-cell (ABC) type DLBCL. No distant metastasis was detected by chest X-ray, intravenous pyelogram, cystoscopy, or colon fiberscopy. Magnetic resonance imaging and contrast-enhanced computed tomography (CT) revealed a large soft tissue mass with central necrosis involving the posterior vaginal wall (Figure 2). PET-CT revealed an increased ^{18}F-fluorodeoxyglucose focal uptake in the vaginal mass. Distant metastases or lymph node involve-

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Table 1. — *Immunocytochemical analyses of DLBCL of the vagina*.

Author (Year)	CD5	CD10	CD20	Bcl–2	Bcl–6	MUM–1	CD79a	Ki–67
Guarini *et al*. (1999) [4]	NE	NE	+	–	NE	NE	+	NE
Domingo *et al*. (2004) [6]	NE	NE	+	–	NE	NE	NE	–
Mahendran (2008) [7]	NE	–	+	NE	+	NE	NE	NE
Ikuta *et al*. (2010) [8]	–	–	+	NE	NE	NE	+	+
Nasu *et al*. (present case)	–	–	+	±	+	+	+	NE

Table 2. — *Reported cases of primary vaginal DLBCL treated with R-CHOP*.

Author (year)	Age	Symptom	Ann Arbor stage	Treatment	Follow-up
Cohn *et al*. (2007) [11]	64	Asymptomatic	IE	R-CHOP	AWD 26 mo
	46	Vaginal bleeding Abdominal fullness	IV	R-CHOP	DOD 16 mo
	22	Pelvic pressure Vaginal bleeding	IE	R-CHOP → RT	NED 6 mo
Hussein *et al*. (2007) [12]	79	Vaginal mass	ND	R-CHOP → RT	NED 12 mo
Mahendran (2008) [7]	32	Asymptomatic	IIE	R-CHOP	NED 6 mo
Nasu *et al*. (present case)	44	Vaginal bleeding	IE	R-CHOP → RT	NED 13 mo

AWD, alive with disease; DLBCL, diffuse large B-cell lymphoma; DOD, dead of disease; ND, not described; NED, no evidence of disease; R-CHOP, rituximab + adryamicin + cyclophosphamide + vincristine sulfate + prednisolone; RT, radiation therapy.

ment was not observed by contrast-enhanced CT or PET-CT. The serum level of soluble interleukin-2 receptor was 683 U/ml. Bone marrow biopsy was negative. The patient was diagnosed with Ann Arbor Stage IEA DLBCL and Stage III vaginal cancer, according to the International Federation of Gynecologists and Obstetricians (FIGO) classification system (1971).

Immediately after the diagnosis, the patient was treated by chemotherapy consisting of rituximab (570 mg), adryamicin (75 mg), cyclophosphamide (1,100 mg), vincristine sulfate (2 mg), and prednisolone (500 mg) (R-CHOP). The tumor disappeared completely after three courses of R-CHOP. The serum levels of sIL-2R decreased to within normal limits. After six courses of R-CHOP administration, the patient underwent external irradiation to the whole pelvis (36 Gy). The patient is well without evidence of disease 13 months following the initial treatment.

Discussion

Because of its rarity, there is no established treatment protocol for primary NHL of the vagina. The mainstays of treatment for NHL have been chemotherapy and/or radiation therapy, and the majority of cases of vaginal DLBCL presented in the literature were also treated with chemotherapy and radiation therapy [5]. Standard chemotherapy treatment includes a CHOP regimen for at least three cycles, with a minimum of six cycles for bulky disease, followed by radiation therapy. It has been reported that DLBCL of the vagina responds very well to this protocol, with a 70-90% cure rate, especially in the early stages [5]. However, the use of novel treatments, including monoclonal antibodies, is being assessed and becoming a standard of treatment [9]. The addition of the anti-CD20 monoclonal antibody, rituximab, to CHOP (R-CHOP) has led to a marked improvement in the survival of patients with DLBCL [10]. However, as shown in Table 2, there have been only five cases of vaginal DLBCL treated with R-CHOP previously reported in the literature [7, 11, 12].

DLBCL is heterogeneous both clinically and morphologically. Patients with DLBCL have highly variable clinical courses: although most patients respond initially to chemotherapy, fewer than half of the patients achieve a durable remission [13]. Although a combination of clinical parameters of the International Prognostic Index (IPI) is currently used to assess a patient's risk profile, these prognostic variables are considered to be proxies for the underlying cellular and molecular variation within DLBCL [14]. DLBCL can be divided into two prognostically significant subgroups, germinal center B-cell- like (GCB) and ABC-like [15]. Initially, a third subgroup (simply termed type 3) was also defined. This was based on a collection of cases that could not be classified into either the GCB- or ABC-subgroup and does not represent a distinct subgroup [16]. The GCB group has a significantly better survival than the ABC group, with the 5-year survival rates being 15-30% and 50-60%, respectively [17]. Although the type 3 group is heterogeneous and not well defined, it is suggested to have a poor outcome similar to the ABC group [15].

The subclassification of DLBCL by CD10, Bcl-6, and interferon regulatory factor (IRF) 4/MUM1 expression has been proposed [18]. Cases with CD10 expression in > 30% of cells are regarded as GC type as well as cases that are CD10-, Bcl-6+, IRF4/MUM1-. All other cases are regarded as of non-GC type [18]. Hans *et al*. [18] reported that the 5-year overall survival for the GCB group was 76% compared with only 34% for the non-GCB group, which is similar to that reported using a cDNA microarray [15]. The addition of other markers such as Bcl-2 and cyclin D2 may lead to an improvement in the immunophenotypic subgrouping of DLBCL [19]. It has been demonstrated that the expression of Bcl-6 or CD10

Fig. 1

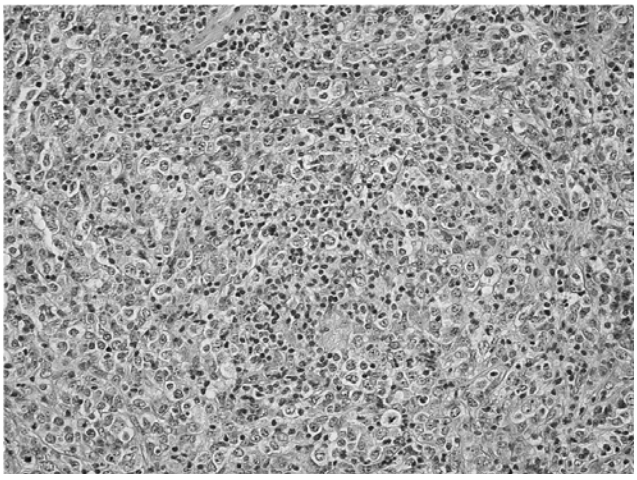

Figure 1. — Histological findings of the biopsied specimen. The tumor tissue consisted of fragments of tissue composed solely of diffuse sheets of large atypical lymphoid cells. These cells contained vesicular nuclei with prominent nucleoli and clear cytoplasm. Histiocytes and small mature lymphocytes were interspersed throughout the tumor tissue (hematoxylin and eosin staining, original magnification x200).

Fig. 2

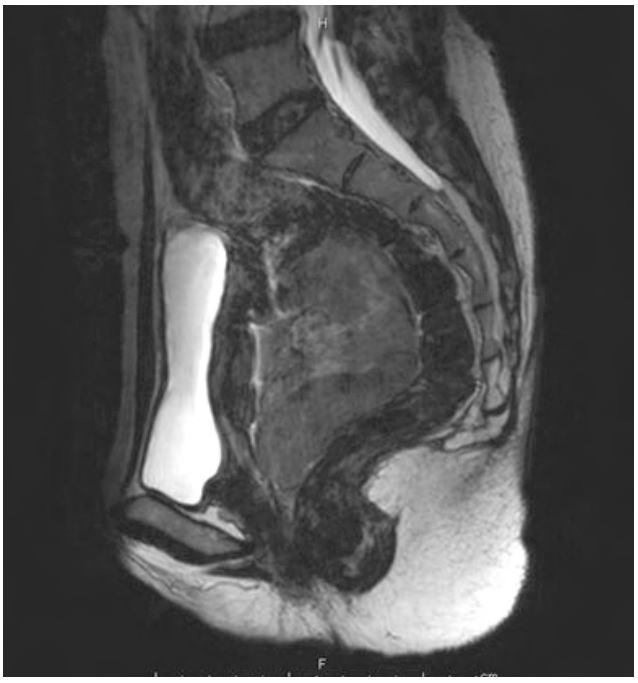

Figure 2. — Magnetic resonance imaging findings. T2-weighted images revealed a high intensity mass (97 x 63 mm) located in the posterior vaginal wall.

was associated with better overall survival, whereas expression of MUM1, Bcl-2, or cyclin D2 was associated with worse overall survival [18]. The addition of the anti-CD20 antibody, rituximab, to the conventional chemotherapy was reported to have eliminated the negative impact of the expression of Bcl-2 and the positive impact of Bcl-6 on clinical outcome [10, 20, 21]. However, the use of immunohistochemical panels to assign prognostic groups does not currently have a role in routine clinical practice [17], especially in DLBCLs arising in the vagina. As shown in Table 1, there have been only four cases of vaginal DLBCL with detailed immunophenotypic subgrouping.

In summary, we presented an additional case of vaginal DLBCL that was subgrouped as ABC type and successfully treated by chemotherapy, R-CHOP, followed by pelvic irradiation. As discussed above, little attention has been paid to the use of rituximab in addition to conventional chemotherapy or to the importance of clinical and morphological subgrouping of DLBCL arising in the vagina. It is important to evaluate the effects of rituximab on the prognosis of vaginal DLBCL. In addition, clinical use of immunophenotypic subgrouping should be considered for vaginal DLBCL.

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