



Case report

Malignant lymphoma of the cervix in a bicollis uterus considered to be a post-transplant lymphoproliferative disorder in a patient after renal transplantation: A case report

Yu Yoshida^{*}, Ririko Izumi, Saki Iwashita, Natsumi Nakashima, Kaori Kishida, Yuzo Imachi, Yukiyo Shimada, Kana Maehara, Tomoko Wada, Mariko Ando, Yoichiro Hamasaki, Shuichi Kurihara, Sachiko Onjo, Makoto Nishida

Department of Obstetrics and Gynecology, Japanese Red Cross Fukuoka Hospital, 3-1-1 Ohgusu, Minami-ku, Fukuoka 815-8555, Japan

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ABSTRACT

Post-transplant lymphoproliferative disorder (PTLD) refers to a group of diseases, characterized by abnormal proliferation of lymphocytes, that develop after organ transplantation. PTLD is associated with poor prognosis, and has become a major problem for transplant patients. In this report, we described a case of malignant lymphoma of the cervix in a bicollis uterus considered to be a PTLD in a patient after renal transplantation. The incidence of this disease is expected to increase as the survival rate of transplant patients improves. Hence, it is very important for gynecological oncologists to consider the presence of PTLD when examining such patients.

1. Introduction

Post-transplant lymphoproliferative disorder (PTLD) refers to a group of diseases, mainly characterized by abnormal proliferation of lymphocytes that develop after organ transplantation. PTLD is associated with poor prognosis; following the increase in the number of long-term survivors after transplantation, this disease has become a major problem. In this report, we describe a case of malignant lymphoma of the uterine cervix considered to be a PTLD in a patient after renal transplantation.

2. Case presentation

A 47-year-old, gravida-3, para-3 Japanese woman presented to our hospital with persistent atypical genital bleeding. The patient had been diagnosed with immunoglobulin A nephropathy after her first childbirth and received a living-donor renal transplant for end-stage renal failure at the age of 30. She had been receiving cyclosporine (CyA) 200 mg/day and azathioprine 50 mg/day after renal transplantation. Her family history was unremarkable, her performance status (ECOG) was 0, and the superficial (cervical, supraclavicular, axillary and groin) lymph nodes were not palpable. She did not report fever, night sweats, or weight loss. Vaginal speculum examination revealed a complete vaginal septum and two distinct cervixes, thought to be a bicollis uterus. The

right cervix was normal in appearance; however, the left cervix was replaced with an easily bleeding mass (Fig. 1A, B). Pelvic examination revealed that the bilateral parametrium was not indurated. Transvaginal ultrasound evaluation showed a hyperechoic tumor in the left cervix, and detected a uterus with two distinct uterine horns, each with a separate endometrial cavity. Pelvic magnetic resonance imaging showed a 4-cm mass in the left cervix, and abdominal computed tomography revealed multiple lymphadenopathies in the pelvis without definite distant metastasis (Fig. 2A, B). Her serum level of soluble interleukin-2 receptor was elevated (901 U/mL), while that of lactate dehydrogenase was modestly elevated (297 IU/L).

Cytological examination of the left cervix was positive for malignant cells, showing a large amount of scattered atypical cell with a high nucleus-to-cytoplasm (N/C) ratio (Fig. 3A). Histological examination of the cervical tumor showed diffuse proliferation of malignant cells with basophilic cytoplasm and severely atypical nucleus. The N/C ratio of these cells was very high (Fig. 3B). Immunohistochemistry revealed that the malignant cells were strongly positive for CD20, suggesting that the tumor was a B-cell lymphoma (Fig. 3C). A bone-marrow biopsy was performed for further examination, which did not show bone marrow infiltration. The Epstein-Barr virus (EBV) receptor of the patient was negative. We finally reached the diagnosis of diffuse large B-cell lymphoma (Ann Arbor classification stage IIEA). Based on her past history of renal transplantation, the tumor was considered to be PTLD.

^{*} Corresponding author.

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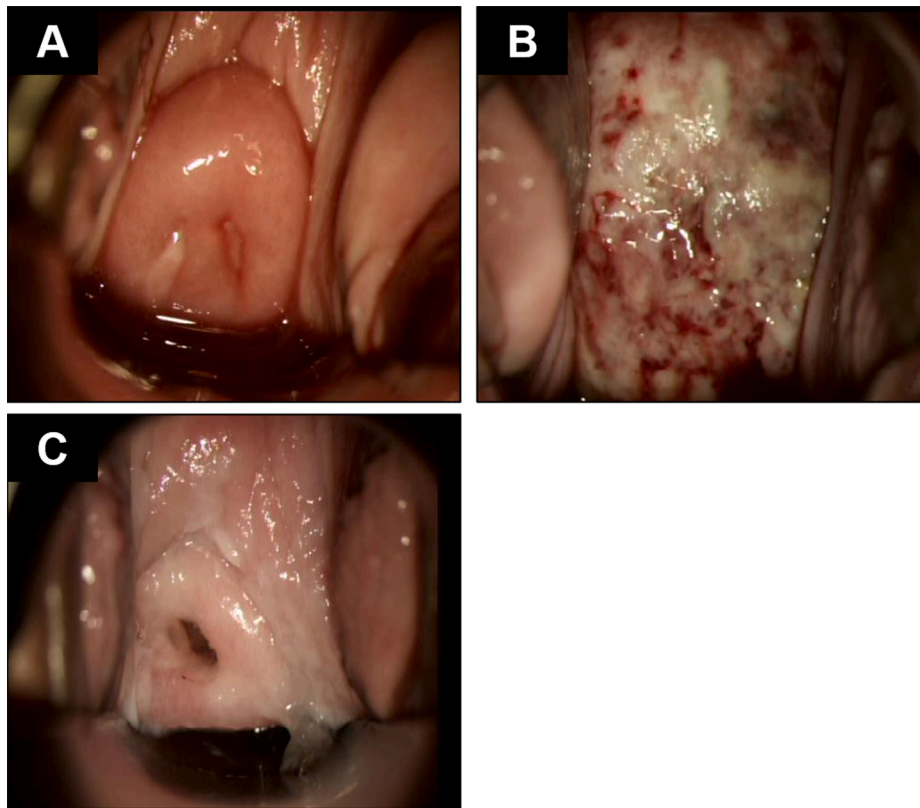


Fig. 1. Macroscopic findings of the uterine cervixes. The right cervix was normal in appearance (A), but the left cervix was replaced with an easily bleeding mass (B). The left cervical tumor disappeared after initial R-CHOP therapy (C).

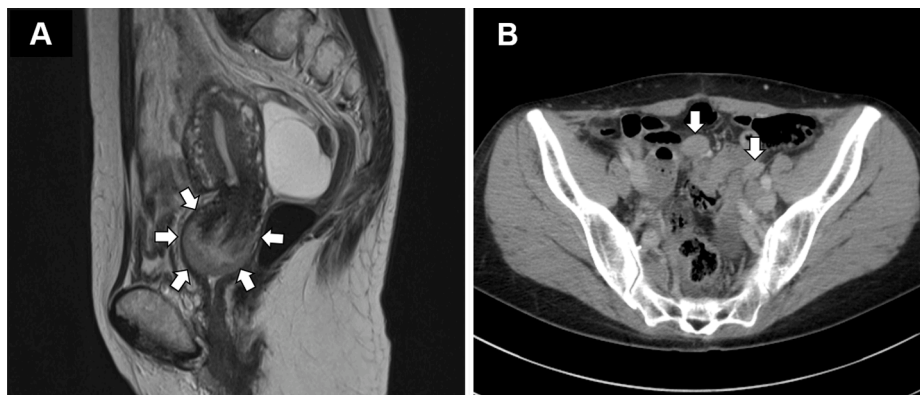


Fig. 2. MRI and CT findings prior to treatment. Pelvic MRI showed a 4-cm mass in the left cervix (A), and abdominal CT revealed multiple lymphadenopathies in the pelvis (B). MRI, magnetic resonance imaging; CT, computed tomography.

Six cycles of R-CHOP therapy were performed (triweekly cyclophosphamide 750 mg/m², vincristine 1.4 mg/m², doxorubicin 50 mg/m², rituximab 375 mg/m² were administered on day 1, and prednisolone 100 mg/body was administered from days 1–5), together with reduction of CyA to 100 mg/day considering that the tumor was likely to be a PTLD. The cervical lesion disappeared after the first cycle of R-CHOP therapy (Fig. 1C). She experienced severe myelosuppression after the first cycle. We discontinued the oral administration of azathioprine because it may have been partly responsible for the observed myelosuppression. Three years following the six cycles of R-CHOP therapy, the patient remains in remission.

3. Discussion

Great progress has been made in the surgical and medical aspects of transplantation therapy over the past few decades. Currently, both solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) have been well-established therapeutic options for patients with end-stage organ failure or a variety of hematological disorders, respectively. These contributed to an increase in the long-term survival of transplant recipients. PTLD is a type of lymphoproliferative disease that develops under extrinsic immunosuppression following organ transplantation; Doak et al. (1968) reported the first case of PTLD in 1968. Lifelong treatment with immunosuppressants is required for transplant recipients to protect the allografts; hence, PTLD has become a major problem for post-transplant survivors. The presence of PTLD is a

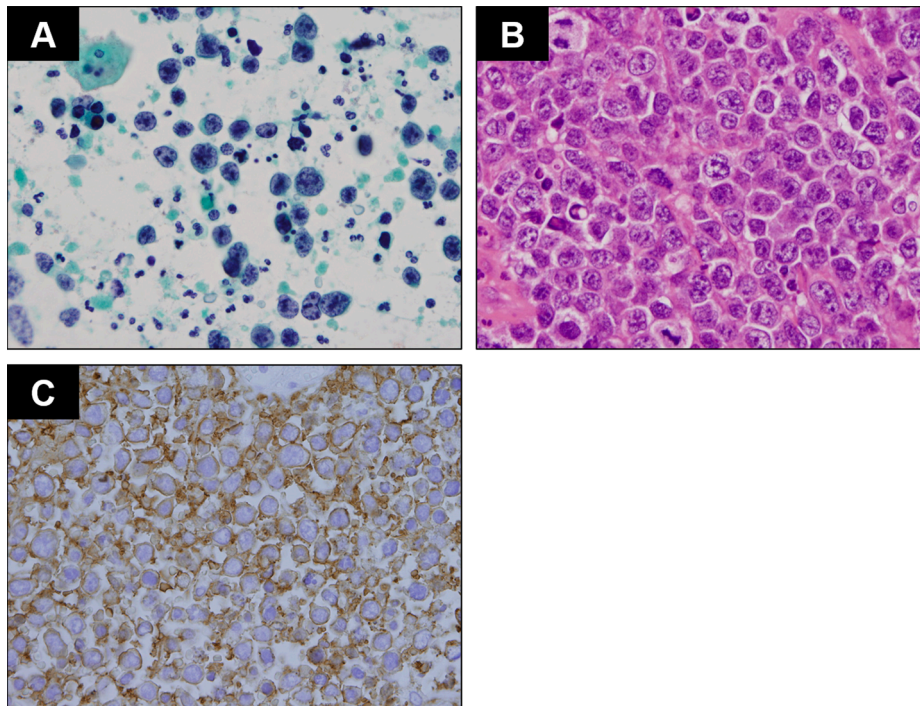


Fig. 3. Cytological examination of the left cervical tumor showed a large amount of scattered atypical cells with a high N/C ratio (A: 100 \times). Histologically, the tumor cells with a basophilic cytoplasm and severely atypical nucleus proliferated diffusely. The N/C ratio of these cells was very high (B: HE 100 \times). Immunohistochemistry revealed that the malignant cells were strongly positive for CD20 (C: CD20 100 \times). HE, hematoxylin-eosin.

poor prognostic factor in transplant recipients. [Uhlin et al. \(2014\)](#) reported that the 3-year survival rate after HSCT among patients who developed PTLD was only 20% versus 62% among those without PTLD. The organ-specific incidence is higher for transplants that require treatment with more potent immunosuppressants. The highest incidence of PTLD is observed in patients after HSCT (as high as 20%). In patients who undergo SOT, PTLDs also develop in 20% of cases after intestinal or multi-organ transplantation. Although kidney is the most frequently transplanted solid organ, fortunately, the incidence of PTLD in these patients is relatively low (1–5%) ([Taylor et al. 2005](#)).

It is well known that the incidence of malignant tumors is extremely high in the immunosuppressive state after SOT or HSCT. It has also been reported that human papillomavirus-related lesions (cervical intraepithelial neoplasia) in patients after organ transplantation do not regress as spontaneously as in the general population ([Tanaka et al. 2016](#)). Notably, the incidence of primary lymphoma arising in the female genital tract is very low, comprising 0.2–1.1% of all cases of extra nodal lymphoma ([Nasioudis et al. 2017](#)). Therefore, it is unlikely that PTLD will develop in the female genital tract. The reported number of cases of PTLD in the female genital tract remains limited, although more than 5 decades have passed since the first report of PTLD. Few cases of PTLD involving the ovaries have been reported ([Einollahi et al., 2008](#); [Inoue et al., 2010](#)). With regard to the uterine cervix as the primary site of PTLD, only one case of non-Hodgkin B-cell lymphoma in 67-year-old woman after liver transplantation has been reported ([Nagarsheth et al. 2005](#)).

PTLD is a disease spectrum with various phenotypes, ranging from benign lesion-like reactive lymphadenitis to malignant lymphoma. According to the latest 2016 World Health Organization classification, PTLT has been subclassified as plasmacytic hyperplasia PTLT, infectious mononucleosis PTLT, florid follicular hyperplasia PTLT, polymorphic PTLT, monomorphic PTLT (B- and T-/NK-cell types), and classical Hodgkin lymphoma PTLT. Most cases of PTLT are derived from B cells; in addition, it is well established that PTLT is involved in primary infection or reactivation of EBV in the majority of cases. Oncogenic EBV plays an important role in pathogenesis through multiple mechanisms.

Treatment of PTLD varies according to the severity of the disease, histological features, and status of EBV infection. In the only reported case of PTLD arising from the cervix, the patient was treated with surgical excision of the focal PTLD lesion ([Nagarsheth et al. 2005](#)). She underwent extended surgical treatment but did not receive adjuvant therapy except for tapering of immunosuppressive therapy and was disease-free 4 years after surgery. In recent years, reduction of immunosuppressive therapy and/or administration of rituximab have become the primary treatment options in numerous cases, although the former must be carefully performed to prevent allograft loss. Other treatment options include donor lymphocyte infusion, cytotoxic chemotherapy, and radiotherapy ([Abbas et al. 2020](#)). Surgical resection is recommended only for refractory and localized PTLD cases. In general, early-onset EBV-positive PTLD is often associated with a favorable prognosis, whereas late-onset EBV-negative PTLD is linked to a poor prognosis ([Nelson et al. 2000](#)). In the present case, PTLD occurred 17 years after renal transplantation and the EBV infection status was negative. Fortunately, R-CHOP therapy was very effective against the tumor in this case, and the dose reduction of CyA by 50% did not adversely influence the transplanted kidney.

Nevertheless, it is expected that the incidence of PTLD will increase as the survival rate of transplant patients improves. Hence, it is very important for gynecological oncologists to consider the presence of PTLD when examining such patients.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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