Non-Hodgkin's Lymphoma of the Vaginal Wall in a Hemodialysis Patient with Hepatocellular Carcinoma

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Abstract: A 66 year old woman with end-stage renal disease and liver cirrhosis due to chronic hepatitis C virus infection was introduced to hemodialysis therapy in 2003. In 2007, hepatocellular carcinoma was identified and the patient underwent radio frequency ablation (RFA) and ethanol injection therapy (EIT) under laparotomy. A large vaginal tumor was incidentally found at gynecological examination. Histological diagnosis was diffuse large B-cell lymphoma (Stage IE). During the first course of chemotherapy, the vaginal tumor began to prolapse from the vaginal wall due to an excellent response to the chemotherapy and finally was resected. The patient received another course of chemotherapy followed by radiotherapy. The vaginal tumor was undetectable in the follow-up imaging studies. Although patients with end-stage renal disease are at increased risk for several cancers, the occurrence of malignant lymphoma following hepatocellular carcinoma is rare. Furthermore, lymphomas arising from the female genital tract are very uncommon.

Key words: hemodialysis, hepatocellular carcinoma, malignant lymphoma, vagina.

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Introduction

Patients treated by dialysis for end-stage renal disease (ESRD) have been reported to have an increased risk of cancers [1-3], especially those of the kidney and urinary tract [4, 5]. Several studies reported the increased incidence of primary liver cancer, which is consistent with the high prevalence of hepatitis C in dialysis patients in the majority of countries [4, 6]. Regarding the incidence of cancers of the tongue, colon, breast, and uterine cervix, results were conflicting [1, 2, 4, 6]. Although one early report [7] and two recent studies [4, 6] suggested the excess of non-Hodgkin's lymphoma among dialysis patients, other studies failed to confirm those findings [1, 8]. Here we report a case with malignant lymphoma arising from the vaginal wall in a female hemodialysis patient in the course of hepatocellular carcinoma (HCC). The occurrence of malignant lymphoma following HCC is rare. Furthermore, lymphomas arising from female genital tract are very uncommon.

Case Report

A 66 year old woman with ESRD resulting from chronic glomerulonephritis commenced thrice-weekly hemodialysis (HD) therapy in 2003. Physical examination at the start of HD identified massive ascites. Subsequent serological tests and the results of imaging studies confirmed that the patient had liver cirrhosis due to chronic hepatitis C virus (HCV) infection. In 2007, an ultrasound sonography and computed tomography (CT) with contrast enhancement identified a HCC measuring 9 mm in diameter adjacent to the right hepatic vein. The patient underwent radio frequency ablation (RFA) therapy and ethanol injection therapy upon laparotomy, because percutaneous approaches to the HCC seemed difficult and blood flow from the hepatic vein adjacent to the tumor might have reduced the efficacy of percutaneous RFA therapy. A follow-up CT at one year later (August 2008) did not reveal any recurrence of HCC. In addition, there was no pelvic mass.

In January 2009 (five months after the preceding CT), a large vaginal tumor, approximately 5 cm in diameter, was incidentally found at gynecological check up. The patient did not complain of abnormal vaginal bleeding. She had no unexplained fever and no night sweat. Cytologic smears of the tumor were suggestive of malignant lymphoma. Magnetic resonance imaging (MRI) of the pelvis (Fig. 1) revealed a huge vaginal mass with relatively homogeneous signal intensity. The tumor showed a low signal intensity on a T1-weighted and a relatively high signal intensity on a T2-weighted image. High signals suggesting necrosis were not confirmed. Subsequently, the patient underwent a biopsy of the vaginal tumor. On microscopic examination, a diffuse proliferation of large neoplastic cells was seen (Fig. 2). The nuclei had round to oval nucleoli and coarse granular chromatin. Mitoses were occasionally present. Immunostaining revealed that the tumor cells were positive for major B-cell markers (CD19, CD20, kappa light chain, and bcl6, respectively), whereas a T-cell marker, CD45RO, was negative. Histological diagnosis of diffuse large B-cell lymphoma (DLBCL) was made based on the findings of the light microscopy and immunostaining. Workup for staging confirmed that the lymphoma was confined
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Fig. 1. MR imaging of the pelvis (sagittal T2-weighted image). A huge vaginal tumor (arrowheads) showed relatively high signal intensity. (B: bladder, U: uterus)

Fig. 2. Diffuse proliferation of large neoplastic cells was seen. (hematoxylin and eosin.)

Fig. 3. MR imaging of the pelvis after first course of chemotherapy (sagittal T2-weighted image). The huge vaginal tumor was undetectable. (B: bladder, U: uterus)

to a single extra-nodal site (vagina), corresponding to Ann Arbor classification - stage IE.

On admission, the value for serum LDH slightly exceeded the normal range (234 IU/l; reference range 119-229 IU/l), whereas the soluble IL-2 receptor level was significantly elevated (10,700 U/ml; reference range 145-519 U/ml). HCV-associated cryoglobulinemia was not present. Combination chemotherapy (cyclophosphamide, doxorubicin, and prednisolone) with rituximab (anti-CD20 monoclonal antibody) followed by radiotherapy was chosen for her stage IE lymphoma. Doses of cyclophosphamide and doxorubicin were reduced, since the patient had ESRD and liver cirrhosis. She experienced severe infusion reactions during the first administration of rituximab, and thereby rituximab infusion had to be stopped. During the first course of chemotherapy, the vaginal tumor began to prolapse from the vaginal wall due to an excellent response to the chemotherapy and finally was resected. An MRI of the pelvis after the first course of chemotherapy (Fig. 3) demonstrated the disappearance of the tumor. The value for soluble IL-2 receptor was considerably decreased (from 10,700 to 2,850 U/ml). The patient received another course of chemotherapy without rituximab followed by radiotherapy. The vaginal tumor was undetectable in the follow-up imaging studies. The patient remains in complete remission 15 months post treatment, and recurrence of HCC has not been identified so far.
Discussion

*Cancer in hemodialysis patients*

Patients on renal replacement therapy are known to be at risk for developing several cancers [1-3, 9], especially those of the kidney and urinary tract [4, 5, 10]. The increased risk of primary liver cancer (HCC) was also noted in many studies, including a questionnaire survey in Japan [2]. These results could be attributable to the higher prevalence of hepatitis C in dialysis patients in the majority of countries [4, 6]. Furthermore, Maisonneuve et al [4] reported the increased incidence of thyroid cancer and multiple myeloma in a large cohort of 831,804 dialyzed patients from three continents. Although one early report [7] and two recent studies [4, 6] suggested an excess of non-Hodgkin’s lymphoma among dialysis patients, other studies failed to confirm those findings [1, 8]. Therefore it remains uncertain whether patients on dialysis therapy have a greater risk for developing malignant lymphoma. Moreover, the occurrence of malignant lymphoma in Japanese patients on HD seems to be less, since there are only sixteen cases reported in the literature [11]. Accordingly, it appears that the development of non-Hodgkin’s lymphoma in the course of HCC, as in the present case, is quite uncommon.

*Malignant lymphoma of the vagina*

Although lymphoma cells frequently infiltrate into the uterine corpus and cervix and vagina in cases of advanced disease or in patients who died of malignant lymphoma [12, 13], the female genital tract is only rarely the initial site of recognized involvement. In a review of 8,767 cases of lymphomas other than Hodgkin’s disease by Freeman et al [14], only 16 patients (0.18%) presented with lymphoma arising in the female genital tract. In a review of approximately 9,500 women with lymphoma from the Armed Forces Institute of Pathology, there were only 15 cases (0.16%) of lymphoma originating in the corpus uteri, cervix and vagina [15]. Malignant lymphoma of the vagina is further rare. Approximately 40 cases have been reported in the literature to date [16, 17]. To our knowledge, the present case report is the first description of vaginal lymphoma in a patient on maintenance HD.

Regarding the presenting symptoms of vaginal lymphoma, abnormal vaginal bleeding is commonest in many reports [13, 18-20]. Other patients presented with abdominal or pelvic masses, urinary dysfunction, and vaginal discharge [15, 20]. Of note, a few cases were asymptomatic [20, 21], as in the present case.

Immunophenotyping studies more than two decades ago have already shown that the majority of vaginal lymphoma was of B-cell lineage [18]. Similar to our case, diffuse large B-cell lymphoma (DLBCL) was the most frequent type (62.1% to 77.8%) in recent studies [16, 17, 20, 21].

In our patient, the lymphoma was confined to the vagina, which corresponds to Ann Arbor classification - stage IE. This is in agreement with a previous study [21] demonstrating that the majority of cases were at lower stages (stage IE or IIE). Furthermore, the proportion of stage IE has been reported to be as much as 70% [20, 22].

A few studies have described the MRI features of vaginal lymphoma. On T1-weighted image, lymphoma produced a homogeneous low signal and a relatively high signal on T2 weighted im-
age [23, 24]. The present case showed similar features on MRI. Relatively homogeneous signal intensity in spite of large tumor size and absence or scantiness of a high signal suggesting necrosis would also be specific MRI findings of vaginal lymphoma, as reported in uterine lymphoma [25, 26]. The information provided by MRI was superior to CT in defining the extent of tumor invasion and confirming non-epithelial origin of the tumor [23, 24].

With respect to the treatment, combination chemotherapy with or without radiotherapy has been used frequently [22]. For a localized disease (stage IE), chemotherapy and radiotherapy is the appropriate treatment [21]. When lymphoma is of B cell origin, addition of rituximab (anti-CD20 monoclonal antibody) to chemotherapy is considered. In the present case, however, administration of rituximab had to be stopped because of severe infusion reaction.

Malignant lymphoma of the uterus and vagina appear to have a relatively favorable prognosis [15, 18]. The most important factor influencing survival is the stage of the disease according to the Ann Arbor classification [22]. A review of the literature shows that a favorable prognosis of localized disease (stage IE) seems to be a common experience [27]. In a review of the literature, Lonardi et al [28] reported that stage IE vaginal lymphomas reached 80% 5-year survival. Vang et al reported that the 5-year survival rate of 19 patients with primary vaginal lymphoma in the literature was 88% [21]. Our patient also showed a favorable response to chemotherapy and radiotherapy, and the patient remains in complete remission 15 months post treatment.

**HCV infection and B-cell non-Hodgkin’s lymphoma**

Since the first report by Ferri et al [29], the association between HCV infection and idiopathic B cell non-Hodgkin’s lymphoma (NHL) has been inferred. A positive association between HCV infection and NHL has initially been reported in countries with relatively high prevalence of HCV, such as Italy, southern United States, and Japan [30]. A large, European multi-center case-control study of lymphoid malignancies, which included countries with a low prevalence of HCV, also found an elevated NHL risk in HCV-positive persons [31]. Therefore, lymphoproliferative disorders could be considered one of the extrahepatic manifestations of chronic HCV infection [32]. However, the role of chronic HCV infection in the development of lymphoma in patients with ESRD is uncertain. So far as we know, one study from Italy evaluated the extrahepatic manifestations of HCV infection in dialysis patients [33]. Among 61 anti-HCV positive patients, only one patient died of NHL [33]. As mentioned, occurrence of malignant lymphoma in Japanese patients on HD seems to be less [11], despite a more than 10% prevalence of HCV infection in this cohort. Accordingly, the significance of chronic HCV infection for the development of NHL among dialysis patients remains open to debate.

In summary, we report here the rare occurrence of non-Hodgkin’s lymphoma of the vaginal wall in the course of HCC in a patient on chronic HD. The patient achieved complete remission after two courses of chemotherapy followed by radiotherapy. Careful surveillance of the patient is necessary since she has two malignant neoplasms.
References

肝細胞癌を有する血液透析患者に発生した膣原非ホジキンリンパ腫

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要旨：C型肝炎による肝硬変を有する66歳の女性は、2003年末期腎不全にて血液透析を導入された。2007年肝細胞癌が発見され、開腹でラジオ波焼灼療法、エタノール注入療法を受けた。2009年1月婦人科検診にて膣腫瘍が偶然発見され、びまん性大細胞型B細胞リンパ腫（stage IE）と診断された。化学療法による腫瘍縮小効果が顕著で、初回治療中に腫瘍からの脱出を認めため切除した。2ケール目の化学療法と放射線療法をもって治療を終了した。経過観察中の画像診断にて、膣腫瘍は同定出来ない状態を維持している。末期腎不全患者では、いくつかの癌の発生リスクが高いため報告されているが、肝細胞癌に続く悪性リンパ腫の発生は稀である。また、女性生殖器原発の悪性リンパ腫は非常に稀である。

キーワード：血液透析, 肝細胞癌, 悪性リンパ腫, 膣。

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