Rituximab-containing Chemotherapy (R-CHOP)-induced Kaposi’s Sarcoma in an HIV-negative Patient with Diffuse Large B Cell Lymphoma

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Abstract

Rituximab treatment may cause or exacerbate Kaposi’s sarcoma (KS) in patients with human immunodeficiency virus (HIV)-associated multicentric Castleman’s disease. Despite the widespread use of rituximab, rituximab-induced KS has not yet been reported in HIV-negative patients with diffuse large B cell lymphoma (DLBCL). We herein report a case of KS that developed after undergoing rituximab-containing chemotherapy in an HIV-negative patient with DLBCL. An 84-year-old man who received rituximab-containing chemotherapy for the treatment of DLBCL developed severe infection, and subsequently KS. Our observations indicate that serious infections under rituximab treatment may trigger KS. KS should therefore be considered when skin tumors appear in lymphoma patients receiving rituximab-containing chemotherapy.

Key words: diffuse large B cell lymphoma, rituximab, Kaposi’s sarcoma, HIV, pneumonia


Introduction

Kaposi’s sarcoma (KS) is a low-grade mesenchymal angioproliferative disorder occurring most commonly in immunocompromised individuals, such as human immunodeficiency virus (HIV)-infected patients or organ transplant recipients (1). KS is caused by the lytic replication of human herpesvirus type 8 (HHV-8/Kaposi’s sarcoma-associated herpesvirus). HHV-8 has also been associated with the pathology of primary effusion lymphoma (PEL) (2) or HIV-associated multicentric Castleman’s disease (HIV-MCD) (3). The introduction of highly active antiretroviral therapy (HAART) (4) has dramatically decreased the incidence of KS among HIV patients, which indicates that the patient’s immune status is a critical determinant of KS development.

Rituximab is a chimeric murine/human immunoglobulin G anti-CD20 monoclonal antibody that is used for the treatment of B cell lymphoproliferative disorders (5). Rituximab depletes CD20⁺ B cells through complement-dependent and antibody-dependent cell-mediated cytotoxicity, thereby exhibiting an anti-tumor effect. Rituximab is currently used in the treatment of several autoimmune diseases, such as rheumatoid arthritis (RA) (6), systemic lupus erythematosus (SLE) (7), and antineutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis (8).

Rituximab therapy may exacerbate KS in patients with HIV-MCD, probably by further suppressing the immune system of immunodeficient HIV-infected patients (9). Rituximab-related KS has been reported in a few HIV-negative patients with MCD (10-14), thus indicating that, at least in some cases, rituximab may directly activate lytic HHV-8 replication and thereby induce the development of KS in the absence of HIV infection. Diffuse large B cell lymphoma (DLBCL) is a common form of non-Hodgkin lymphoma that usually develops in immunocompetent patients. An R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen is the
standard therapy for newly diagnosed patients with DLBCL. Despite the wide use of rituximab for the treatment of DLBCL, KS has not yet been reported in such patients receiving R-CHOP. We herein report, for the first time, a case of KS that developed after R-CHOP treatment in an HIV-negative patient with DLBCL.

**Case Report**

An 84-year-old Japanese man with a history of hypertension and chronic heart failure developed advanced stage (clinical stage IIIA) DLBCL. He did not have a history of recurrent infections. Immunohistochemical studies of affected lymph node biopsy specimens showed the CD20-positive DLBCL cells to be negative for Epstein-Barr virus encoded small RNA (EBER) (Fig. 1). At diagnosis, both the immunoglobulin levels and the absolute lymphocyte count were within normal limits (IgG, 1,266 mg/dL; IgA, 260 mg/dL; IgM, 47 mg/dL; 2,500/mm$^3$ lymphocytes). He received a total of seven cycles of dose-reduced R-CHOP (rituximab 375 mg/m$^2$, cyclophosphamide 600 mg/m$^2$, doxorubicin 40 mg/m$^2$, vincristine 1.1 mg/m$^2$, and oral prednisolone 40 mg/m$^2$) on days 1-5, on a 21 day schedule, which resulted in the complete remission of lymphoma. The patient thereafter developed bacterial pneumonia and subsequent cytomegalovirus (CMV) viremia after seven cycles of R-CHOP, requiring 2 weeks of tracheal intubation and mechanical ventilation. He had 344 CMV pp65 antigen-positive cells per 50,000 neutrophils. After the complete resolution of the pneumonia, several small purple-blue plaques first appeared on the left foot, which thereafter gradually became enlarged, and later spread to the right arm and the genital area (Fig. 2).

The patient had a white blood cell count of 7,800/mm$^3$ with 2,256/mm$^3$ lymphocytes (525/mm$^3$ CD4$^+$, 1,316/mm$^3$ CD8$^+$ and 5/mm$^3$ CD20$^+$ cells), thus indicating well preserved CD4$^+$ T cell counts and substantially low B cell counts. He had hypogammaglobulinemia (IgG, 467 mg/dL; IgA, 68 mg/dL; IgM, 14 mg/dL). He was negative for the HIV antibody. Resected plaque specimens showed the histologic features of KS (Fig. 3). The proliferating spindle-shaped cells expressed CD31, CD34, D2-40 (a marker of lymphatic endothelium), and latency-associated nuclear antigen-1 (LANA-1, a diagnostic marker for KS), but did not express Factor VIII or EBER. LANA-1 is an HHV-8 encoded protein highly expressed in latently infected tumor cells and its expression has been found to be a highly sensitive and specific marker of KS. A diagnosis of KS was thus made. An immunohistochemical analysis of lymph node biopsy specimens at the initial diagnosis showed the DLBCL cells to be negative for LANA-1 (Fig. 1). No recurrence of KS was observed after resection of all KS lesions and the patient remains in complete remission of DLBCL at the time of this writing (17 months after R-CHOP introduction). However, his immunoglobulin levels are still low (IgG, 666 mg/dL; IgA, 73 mg/dL; IgM, 16 mg/dL).

**Discussion**

KS often develops in immunocompromised individuals, such as organ transplant recipients and acquired immune deficiency syndrome patients. In the present case, rituximab induced the development of KS in a DLBCL patient without HIV infection. At the time of KS diagnosis, the circulating CD4$^+$ cell count was 525/mm$^3$. KS develops most often in patients with less than 150 CD4$^+$ cells/mm$^3$ (15, 16). It is therefore likely that cellular immunodeficiency played only a minor role in the development of KS. On the other hand,
the circulating CD20+ cell count and IgG levels were 5/mm³ and 467 mg/dL, respectively, thus indicating an impaired humoral immunity. We therefore think that rituximab-induced B cell depletion triggered the development of KS in this case.

Despite the widespread use of rituximab, there have been no reported cases of rituximab-related KS in HIV-negative patients with DLBCL. However, the occurrence of new KS lesions or a progression of preexisting lesions is the main adverse event associated with rituximab treatment in patients with HIV-MCD (9). The treatment of HIV-MCD with rituximab results in a reactivation of HHV-8 in 20-50% of patients (9, 17). Therefore, in our case, it is likely that additional factor(s) in addition to rituximab treatment contributed to the development of KS. One possible factor would be opportunistic pneumonia that developed after the seventh course of R-CHOP, since systemic inflammation may promote KS progression (18). In particular, CMV infection in-
duces the pro-inflammatory cytokine interleukin (IL)-6. High serum IL-6 levels are associated with a high risk for KS progression in patients with MCD, immune reconstitution inflammatory syndrome, and autoimmune diseases, or in renal transplant recipients (13, 14, 19, 20). The idea that a transient infectious episode could contribute to the development of KS is supported by the observation that tumor recurrence was not observed in the absence of any specific treatment for KS. It is possible that age-related immunosuppression was associated with the development of KS. However, in patients with HIV, KS has been found to occur most frequently in younger people (usually under 40 years of age) (21, 22). Therefore aging might not be a critical factor for KS development in our patient.

Although the mechanisms underlying rituximab-induced KS have not yet been fully elucidated, rituximab-mediated B cell depletion is thought to induce latent HHV-8 reactivation and therefore enhance KS progression (23). In addition, the rituximab-induced depletion of HHV-8-infected B cells may enhance the exposure of HHV-8-susceptible endothelial cells to increased levels of HHV-8 (24). In the present case, the serum immunoglobulin levels decreased after R-CHOP treatment, thus indicating an impaired humoral immunity. Since virus-activated cytotoxic therapy using high-dose zidovudine and valganciclovir has been reported to reduce the HHV-8 viral load, as well as control symptoms and reduce adenopathy in patients with MCD (25), we speculate that the use of antiviral therapy against HHV-8 could thus be a possible future choice for rituximab-induced KS. On the other hand, rituximab has been successfully used for the treatment of HIV-8 associated lymphomas and MCD since rituximab targets HHV-8-infected B cells. Further studies are therefore required to elucidate the pathogenesis of rituximab-induced KS and establish its optimal treatment.

The authors state that they have no Conflict of Interest (COI).

References