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Case Report

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Kaposi sarcoma associated with rituximab-based cytotoxic therapy

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Abstract

Kaposi sarcoma (KS) is a low-grade mesenchymal angioproliferative disease, mostly observed in immune compromised patients. KS is mostly encountered in HIV-positive or organ transplant patients. The drugs causing immunosuppression have also been associated with KS. Here, we present a KS experience associated with rituximab-based therapy.

Keywords

Rituximab, Kaposi sarcoma, lymphoma, HHV-8

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Introduction

Kaposi sarcoma (KS) is an angioproliferative disease, mostly observed in immune-compromised patients. KS is mostly encountered in HIV-positive or organ transplant patients. In addition, it has been associated with numerous diseases and drugs causing immune suppression.[1]

In oncology practice, secondary malignancies associated with the primary disease and the treatment modalities can be observed. Due to immune suppression by cancer or chemotherapeutics, cancer patients are prone to KS. In this case report, we present a case of KS that developed potentially related to rituximab-based cytotoxic treatment.

Case report

A 65-year-old male patient, without any comorbidities, presented with the mass in the neck. In the initial evaluation, physical examination revealed multiple enlarged left anterior cervical lymph nodes. Excisional biopsy showed a diffuse large B-cell lymphoma. Further workup for staging concluded a stage IIA disease with cervical and mediastinal lymph nodes. Patient was treated with R-CHOP regimen (rituximab 375 mg/m^2, vincristine 2 mg, cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, methylprednisolone 80 mg for five days, three weekly). After two cycles of therapy, the cervical nodes completely regressed and he had only grade-1 nausea. After four courses of therapy, we had a complete response in positron emission tomography scan. Ten days after fifth cycle of R-CHOP, the patient presented with blue/purple macular lesions on the posterior aspect of the right forearm, posterior of right wrist, on 1st–3rd right toes, 4th and 5th left toes and bilateral heels (Figure 1). There was neither pain nor itching. After a dermatological evaluation, the lesions were biopsied. In the pathological work up, there was spindle cell proliferation with mild to moderate atypia, arranged in vague fascicles and separated by slit-like vessels. A nuclear positivity with HHV-8 and positive staining with CD34 were detected (Figure 2). The pathology concluded a diagnosis of Kaposi sarcoma. HIV testing was negative. Gastroscopy and colonoscopy were normal. There was no evidence of systemic disease. We used the Naranjo scale for the estimation of

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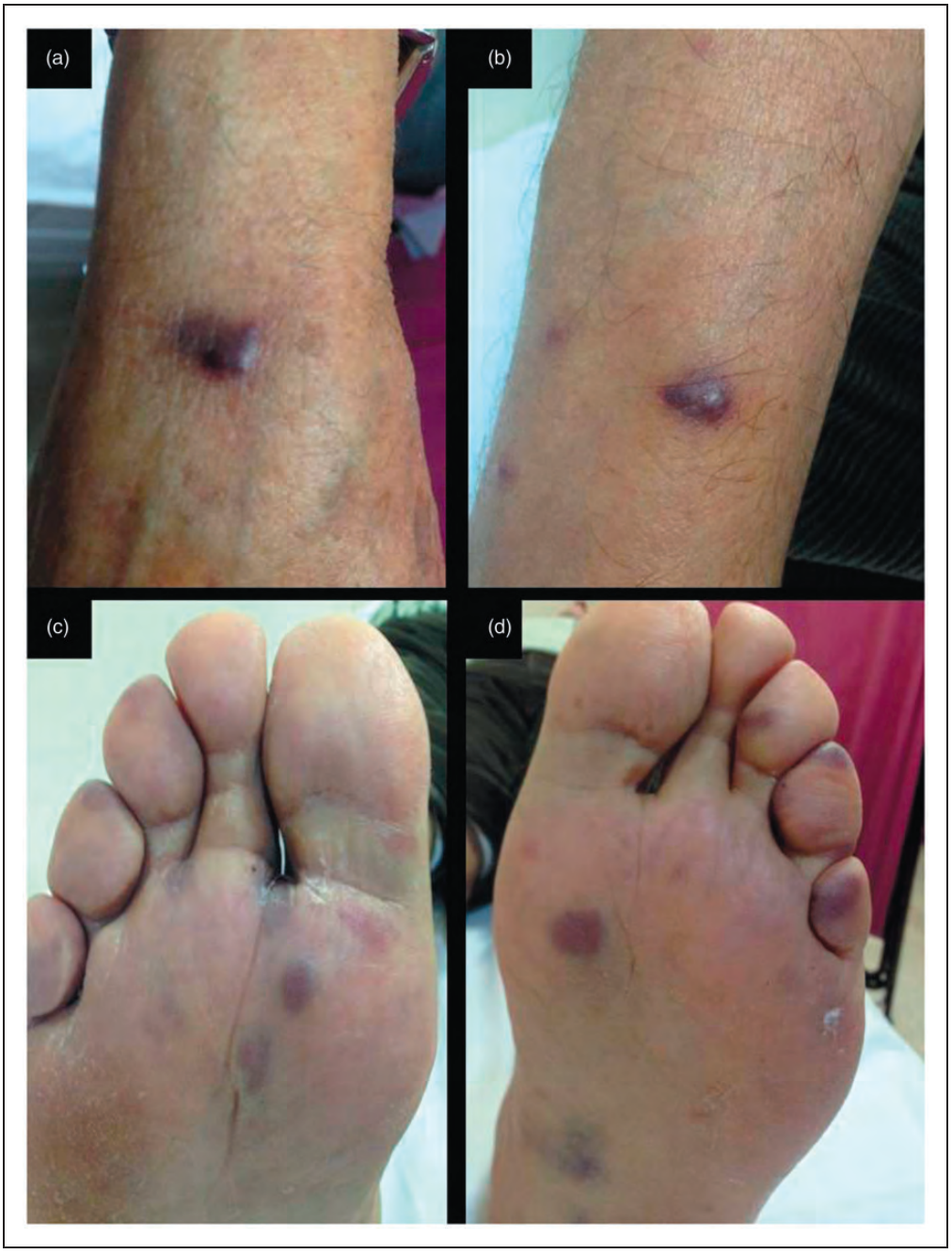

Figure 1. Blue/purple macular lesions on the posterior of the right forearm and posterior of right wrist (a/b), similar blue/purple lesions on 1st–3rd right toes, 4th and 5th left toes and bilateral heels (c/d).

the probability that R-CHOP caused Kaposi sarcoma and the Naranjo scale of our case was 4. So we concluded a "possible drug adverse reaction".[2] The R-CHOP regimen was stopped and the patient was routinely followed for lymphoma. The lesions were treated with radiotherapy and disappeared after treatment. The patient was under remission both for KS and lymphoma after two years of follow-up.

Discussion

Kaposi sarcoma generally presents with purple, red, blue or brown/black macules, plaques and nodules on the skin without pain. Human herpes virus 8 (HHV-8) is the causative agent of KS. However, not all infected persons develop the disease.[3] There are several documented risk factors for clinical KS in a HHV-8 infected

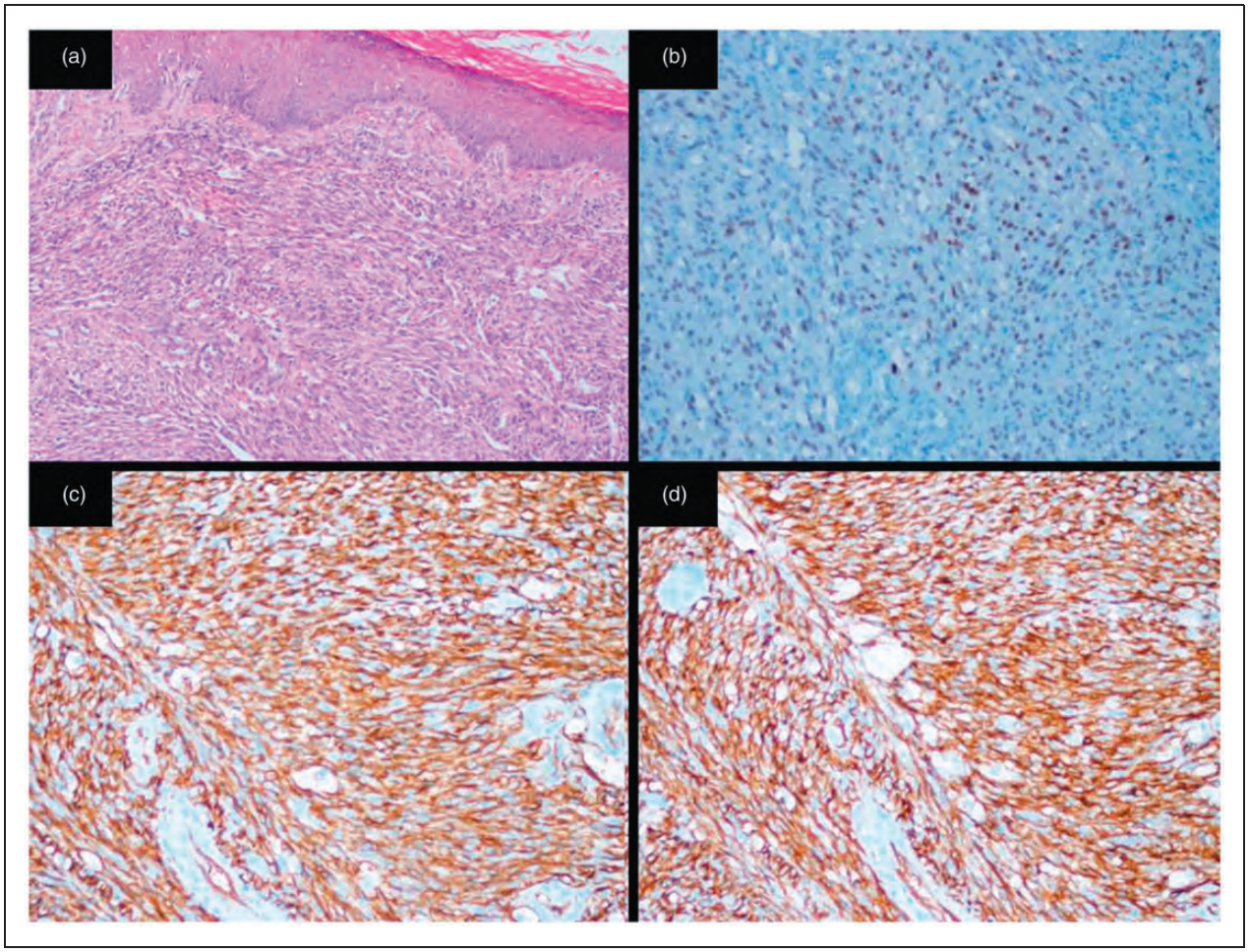

Figure 2. H&E ×10; spindle cell proliferation with mild to moderate atypia, arranged in vague fascicles and separated by slit-like vessels (a), HHV×20; Nuclear positivity with HHV-8 (b), CD34×20; positive staining with CD34 (c), CD31×10; positive staining with CD34 (d).

patient. High HHV-8 lytic and latent antibody titers, immunosuppression, male gender, lymph hematopoietic malignancies have been associated with increased risk for KS.[1] The drugs causing immunosuppression have been associated with KS. Steroids, methotrexate, azathioprine, cyclophosphamide, infliximab and many other drugs that can impair immune defense have been associated with KS.[4,5]

Rituximab, vincristine, cyclophosphamide, doxorubicin and methylprednisolone were used in R-CHOP regimen. Those drugs all have immune suppressive capacity and there is one case of KS that has been associated with R-CHOP regimen.[6] In our case, methylprednisolone 80 mg on days 1–5, on a 21-day cycle. There is no firm association between dose and duration of steroids causing KS. Previous case reports of steroid-induced KS occurred with long-term use.[7,8] Our steroid usage is short-term and interval usage compared to the other cases. There is a case in the literature showing Kaposi sarcoma after cyclophosphamide and steroid treatment.[9] In this report, although the patient continued cyclophosphamide therapy, after discontinuation of steroid therapy, Kaposi lesions improved.

Rituximab is a human/mouse chimeric monoclonal antibody (IgG1) which targets CD20 antigen expressed in more than 95% of normal and malignant B cells, inducing complement-mediated and antibody-dependent cellular cytotoxicity. Rituximab is widely used for autoimmune and hematological disorders. It has been previously reported as a triggering factor for KS.[10,11] In those cases, the patients had a history of KS and they presented with KS flare after rituximab therapy. In addition, similar with our case, there are cases of rituximab-induced KS in HIV-negative patients.[12] In this case report, an elderly gentleman with multicentric Castleman's disease and HHV-8-positive and HIV-negative received treatment with cyclophosphamide, prednisone and rituximab. At the

completion of six cycles, he developed KS which required radiotherapy. The underlying mechanism has been related to the defective T cell mediated-immune defense. Rituximab depletes B cells and causes a decrease in T-cell activation. T-cell activation is significantly decreased following B-cell depletion because of decreased antigen presentation by B cells. In addition, the formation of autoantibodies against T cells can deplete the cellular immunity. So a viral reactivation is inevitable.[13] We are now clear that rituximab causes reactivation of hepatitis B and prophylactic antiviral therapy is recommended.[14] The same scenario has been speculated for KS patients who were under rituximab. Valganciclovir administered orally once per day significantly reduces the frequency and quantity of HHV-8 replication and it is postulated to be used in such high-risk patients to prevent KS flare.[15]

The main difference of our case from other reports was that he did not have a previous history of KS. In this case report, we present a second de novo KS associated with R-CHOP therapy for diffuse B-cell lymphoma.[6] It is the second de novo KS under rituximab therapy in English literature. Our management strategy was similar to the classical KS. While treating patients with rituximab, clinicians should be aware of rare side effects of it and they also should be cautious about secondary primaries.

Declaration of Conflicting Interests

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