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Case Report

Iatrogenic Kaposi Sarcoma: A Case Report in a Non Organ Transplant Patient

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Abstract

Kaposi sarcoma (KS) is an angioproliferative disorder affecting the skin or internal organs and is caused by human herpes virus 8 (HHV8). Four clinical variants have been recognized: classical, African endemic, AIDS-related, and KS caused by iatrogenic immunosuppression. The latter occurring more likely in patients with acquired immunodeficiency syndrome (AIDS) and those undergoing immunosuppressive treatments for organ transplant. However, few studies are related to iatrogenic KS occurring in patients other than organ transplant ones. Although it is unusual that KS occurs in patient with corticosteroids (CS), the hypercortisolism is thought to be associated with development of KS, with spontaneous regression of lesions usually occurring after discontinuation of glucocorticoid therapy, when it possible. Moreover, it can present a therapeutic dilemma, as decreasing the level of immunosuppression may lead to organ rejection in the case of organ transplant recipients, or organ damage in the case of patients with autoimmune disorders. We report a case of a 67 years old HIV-negative man treated by oral corticosteroids and methotrexate for a rheumatoid arthritis who developed an iatrogenic Kaposi's sarcoma.

Introduction

Kaposi sarcoma (KS) is an angioproliferative disorder affecting the skin or internal organs and is caused by human herpes virus 8 (HHV8) [1]. It's a neoplasme first described by Moritz Kaposi in 1872, characterized by low cell proliferation [2]. Four clinical variants have been recognized: classical, African endemic, AIDS-related, and KS caused by iatrogenic immunosuppression [2]. The latter is commonly seen in patients with acquired immunodeficiency syndrome (AIDS) and in organ transplant recipients, and has been reported in patients receiving chronic immunosuppressive therapy [2]. However, few studies are related to iatrogenic KS occurring in patients other than organ transplant ones [3]. Although it is unusual that KS occurs in patient with CS, the hypercortisolism is thought to be associated with development of KS. A number of case reports have noted the development of KS after glucocorticoid therapy for various inflammatory diseases. And most patients show spontaneous regression of lesions after discontinuation of glucocorticoid therapy [2].

We report a case of a 67 years old HIV-negative man treated by oral corticosteroids and methotrexate for a rheumatoid arthritis who developed an iatrogenic Kaposi's sarcoma. Through our case, we highlight the importance to keep in mind this form of Kaposi's sarcoma in patients under chronic immunosupressants (Figure 1).

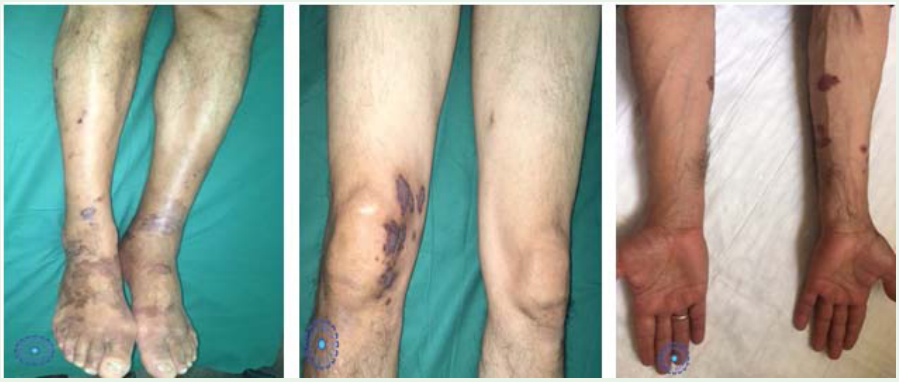

Figure 1: Clinical images showing violaceous and erythematous papules and plaques with irregular and well-defined edges on the lower and upper limbs.

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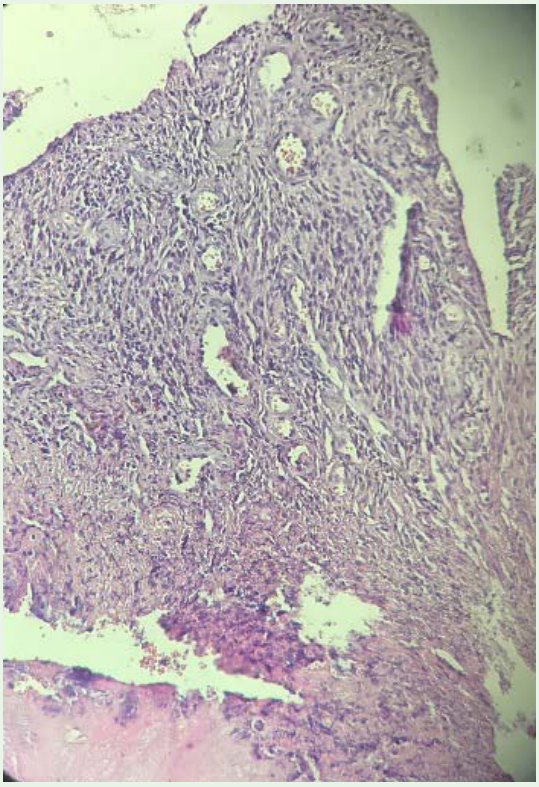

Figure 2: Histological image showing a double proliferation made of vessels and fusiform cells compatible with a Kaposi sarcoma.

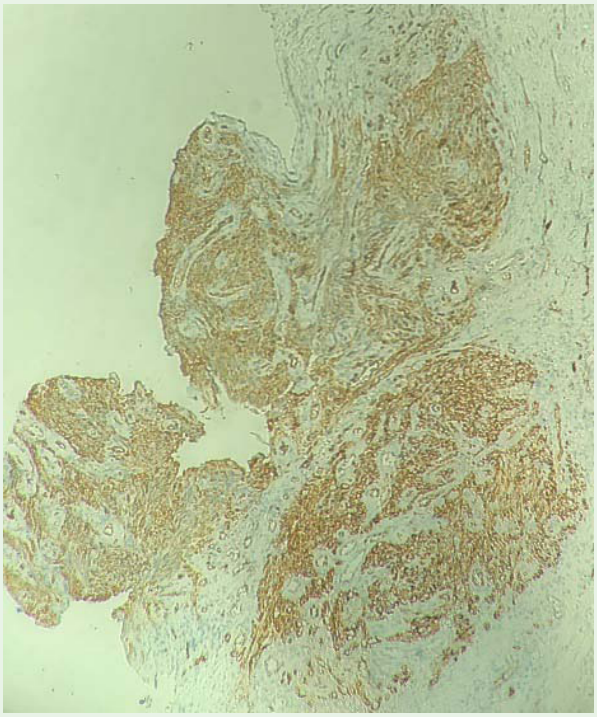

Figure 3: Immunohistochemical stainingshowing positive to human herpes virus 8 (HHV-8), compatible with a Kaposi sarcoma.

Case report

A 67-year-old Moroccan man was seen in our dermatology department with a 4 year history of rheumatoid arthritis treated with oral prednisone at the dose of 30 mg/day in association with Methotrexate 15 mg/ week. The patient was also operated, 3 years ago for a pigmented lesion of the pubis with histology of a Bowen's disease with complete excision of the lesion. The patient developed one year later, new painless bluish-red macules and papules of 5 to 10 mm in diameter on his extremities. No mucous lesion or palpable lymph nodes were noted, neither any reported hemorrhage, gastrointestinal or pulmonary complaints. Cutaneous biopsy were done showing a double proliferation made of vessels and fusiform cellswith an immunohistochemistry positive to human herpes virus 8 (HHV-8), compatible with Kaposi sarcoma (KS). Blood investigations were normal and the whole injury assessment was without abnormalities. Given the limited extent of the lesions, the initial therapeutic attitude was abstention with clinical and paraclinical monitoring with a stationary aspect in our patient during 2 years (Figure 2).

However, 7 months before, the patient reported an extension of his lesions in the legs and thighs with the appearance of new nodular lesions and infiltrated without associated mucosal involvement nor hemorrhagic signs, under oral prednisone at the dose of 10 mg/day and Methotrexate 15 mg/week. Thing that motivated his hospitalization for a new injury assessment, which showed no abnormalities. The decision was to taper down prednisone by 5 mg/d every month then to stop it, and to replace methotrexate with another active non immunosuppressant molecule given the stability of his rheumatoid arthritis. The patient had a slight improvement after tapering down the immunosuppressive therapy with a decline of 10 months (Figure 3).

Discussion

KS is classified in terms of four clearly differentiated variants: classic, endemic, AIDS-related, and iatrogenic [2]. The latter occurring more likely in patients undergoing immunosuppressive treatments, especially calcineurin inhibitors, for organ transplant [3]. However, it has also been reported in other haematological, rheumatological, and pulmonary diseases caused by immunosuppressive treatment [2].

Similar to the classic form, most cases of iatrogenic immunosuppression KS occur in individuals of Mediterranean and Jewish descent according to the infectious rate of HHV-8 in genetically predisposed individuals [4]. This virus has been detected in all forms of KS, including iatrogenic KS [2]. It infects the endothelial cells and remains there in a latent state. When reactivated, it causes aberrant angiogenesis by producing pro-angiogenic Factors [2]. It also exerts its oncogenic effects by inhibiting 2 major tumor suppressor proteins in endothelial cells; the retinoblastoma protein and p53 [2]. However, although HHV-8 infection appears to be necessary, it may not be sufficient for the development of KS without other cofactors, mainly immunosuppression of the host [2]. In fact, decreased immunity leads to the reactivation of HHV-8 [2], which enhances the chances of developing iKS [2].

The prevalence of iKS has grown in the last few years among patients with immune-mediated or proliferative disorders undergoing immunosuppressive therapy [3]. It may appear between one month and 20 years after the immunosuppressive drug is introduced [2], and

is seen 100 and 500 times higher in organ transplant recipients (OTR) than in the general population [3], whereas the incidence is lower in non-organ transplant patients receiving immunosuppressant for another medical condition, with a longer delay of onset of lesions after initiation of treatment [3].

In both classic and immunosuppression-associated KS, clinical presentations are similar, affecting more commonly men and localised preferentially to distal extremities [4]. KS lesions usually appears as brownish macules and plaques, with possibly violaceous exophytic tumors. Some lesions may ulcerate or invade surrounding tissues, such as the bones [2]. Exclusive cutaneous and/or mucosal involvement is usually seen, even though widespread disseminated forms with visceral involvement may be found [3]. The appearance of lesions and their severity vary according to the type of immunosuppressant used, it dosage and the date of onset of treatment, but they are generally regressive when the treatment is stopped [3].

The relationship between iKS onset and immunosuppressants has been shown [3]. Actually, their administration induce the weakening of the immunological surveillance system, thus possibly leading to the development of KS lesions by reactivating a pre-existent HHV8 infection and giving rise to the proliferative transformation of the infected endothelial cells [3]. Among these immunosuppressants, glucocorticoids are associated with the development of KS in transplant recipients, HIV-infected patients, and HIV-negative patients receiving glucocorticoids for autoimmune disorders or chronic inflammatory diseases [2]. It may act indirectly via immune dysregulation by affecting the proliferation of KS cells or directly [2]. In fact, it stimulate the development of growth factors and increases the expression of regulator glucocorticoid receptors on KS cells [3]. Additionally, it indirectly inhibit transforming growth factor beta, a protein that inhibits growth of endothelial cells, thus up regulating KS cell proliferation and inducing KS lesions [2]. Furthermore, excess of glucocorticoids seems to be implicated in activation of HHV-8 replication [4], thus predisposing to opportunistic infections [2]. Other immunosuppressants may induce KS, like CyA that may reactivate HHV8 from latency in tissue cultures and has been related to KS induction or exacerbation [3]. Moreover, high-dose MTX has been suggested as a potential therapy for HHV8-induced prolife rative diseases [1]. However, the extent to which MTX influences reactivation of human herpes viruses is controversial, with some evidence indicating increased reactivation of Epstein Barr virus, but not herpes simplex or Varicella-Zosterviruses [1]. In our case, theremay have been a combination of several additional promoting factors like the use of both CS and MTX that induces this disease, as KS have been reported with such a combined treatment regimen for other skin diseases.

Iatrogenic KS can present a therapeutic dilemma, as decreasing the level of immunosuppression may not be possible or may come at the high cost of organ rejection, such as in the case of organ transplant recipients or organ damage in the case of patients with autoimmune disorders [3]. Even though no exact guidelines on the management of iKS exist to date, reducing or discontinuing immunosuppressants, when it's possible, represents the most accredited therapeutic option in iKS [3]. Regression of KS lesions are noted within 3 to 4 months after that, and though to be due to restoring immune defenses [2]. However, when the immunosuppressant withdrawal cannot be carried out, maintaining the lowest dosage able to successfully control the signs and symptoms related to the underlying disease represents the most advantageous strategy [3]. Additionally, local therapies alone could be considered for localised disease. Vinblastine and bleomycin are first-line chemotherapeutic agents, whereas gemcitabine, etoposide, liposomal anthracyclines, paclitaxel and docetaxel are secondand third-line treatments [3]. Some small case series reported promising results using liposomal doxorubicin in the treatment of iatrogenic KS [2]. In fact, doxorubicin administration may decrease HHV-8 viremia and lead to regression of KS by suppressing cytokine production from infected cells and by inhibiting HHV-8 replication in peripheral blood monocytes [2].

Conclusion

iKS is a HHV-8-associated tumor and must be taken into account for all cases of patients undergoing immunosuppressive therapy, regardless of the drug used, especially in immunocompetent patients, where the use of glucocorticoid should be check. Immunosuppressant reduction/withdrawal, possibly associated with local therapies should represent the first-line treatment. In addition, it require a close multidisciplinary collaboration between dermatologists, oncologists, immunologists and other specialists involved in the underlying diseases management.

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