CASE REPORT

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Kaposi's sarcoma in patients with ulcerative colitis receiving immunosuppressive drugs: Report of a case

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Kaposi's sarcoma is an unusual tumor principally affecting the skin of the lower extremities. Although the association between Kaposi's sarcoma and renal transplant has been well documented, there are few Kaposi's sarcoma cases in the literature associated with ulcerative colitis or other inflammatory bowel diseases. This report presents a patient with ulcerative colitis who developed Kaposi's sarcoma following treatment with long-term medium-dose azathioprine and additional corticosteroids. Kaposi's sarcoma is a rare complication in inflammatory bowel diseases that may (or may not) be related to immunosuppression. Hence, immunomodulatory agents should be planned carefully in the treatment of inflammatory bowel diseases and avoided if they are not essentially necessary. Cases of colorectal Kaposi's sarcoma complicating inflammatory bowel disease should be managed with a conservative approach and discontinuation of the immunosuppressive treatment.

Key words: Ulcerative colitis, Kaposi's sarcoma, immunosuppression, immunomodulatory agents

İmmunosüpresif ilaç alan ülseratif kolitli hastalarda Kaposi sarkomu: Olgu sunumu

Kaposi sarkomu genellikle alt ekstremiteleri etkileyen nadir rastlanılan bir tümördür. Kaposi sarkomu ile renal transplantasyon arasındaki ilişki iyi bilinmesine rağmen literatürde ülseratif kolit veya diğer inflamatuvar bağırsak hastalıklarıyla ilişkili az sayıda olgu bildirilmiştir. Biz ülseratif kolit nedeniyle azathioprine ve ek olarak kortikosteroid tedavisini takiben Kaposi sarkomu gelişen bir vakayı takdim ettik. Kaposi sarkomu immunosüpresyonla ilişkili olarak veya olmayarak inflamatuvar bağırsak hastalığının nadir bir komplikasyonudur. Bundan dolayı immunomodülator ajanlar inflamatuvar bağırsak hastalığının tedavisinde dikkatli planlanmalı ve gerekli olmadıkça kaçınılmalıdır. İnflamatuvar bağırsak hastalığının komplikasyonu olarak ortaya çıkan Kaposi sarkomlu vakalar konservatif yaklaşımlarla yönetilmeli ve immünosupresif tedaviye devam edilmemelidir.

Anahtar kelimeler: Ülseratif kolit, Kaposi sarkomu, immünosüpresyon, immünomodülatör ajanlar

INTRODUCTION

Kaposi's sarcoma (KS) is an unusual tumor principally affecting the skin of the lower extremities (1). It occurs in four clinical forms: classic KS, human acquired immunodeficiency syndrome (AIDS)-related *epidemic* KS, African-type *endemic* KS, and *transplantation-associated* (due to immunosuppression) KS (2). There is a well-known relation between KS and human immunodeficiency virus (HIV) (3). KS was also reported in patients who had immunosuppressive treatment in different settings, such as rheumatoid arthritis, polymyositis/dermatomyositis, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica, Behçet's syndrome, after renal/liver/cardiac transplantati-

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on, Wegener's granulomatosis, and bullous pemphigoid (4-6). In almost all of the cases, human herpesvirus-8 (HHV-8) has a role in KS development (7), and most of them have a history of high-dose and/or long-term immunosuppressive treatment (4). Although KS has been reported in such different rheumatologic settings, it was rarely associated with ulcerative colitis (UC) outside of AIDS or post-transplant states. To our knowledge, only a few cases with UC and KS have been reported.

CASE REPORT

A 42-year-old woman referred to our center with a complaint of newly onset purple-colored lesions on both arms and her face. A diagnosis of UC had been made 13 years earlier, when she had presented with proctitis, rectal pain and bloody stools. The patient was followed regularly by a gastroenterologist. Exacerbations of colitis approximately every 4 to 6 months were treated with mesalamine and intermittent oral corticosteroids; the most recent episode had been treated with a three-month taper of prednisone that ended approximately two months before admission. The patient had been taking azathioprine 100 mg per day for five years without interruption. The immunosuppressive treatment had been given up two days before admission to our hospital due to the sudden appearance of lesions on her arms and face. Red-purple papules were becoming confluent to form a large plaque of 5x5 cm on the anterior side of her left arm and face. The patient had another lesion on her left ankle region that was a 2x2 cm bluish-purple papule with erythema at the base (Figure 1). Physical and laboratory examinations were normal. The patient reported no circumstance requiring long-term sun exposure. No other simultaneous precancerous skin lesions (i.e. nevi pigmentosus) were found in this patient.

Pathologic examination of the lesion on the left arm region revealed early stage KS. Hematoxylin and eosin staining of a section from a biopsied nodule showed moderate chronic inflammation and a focal submucosal proliferation of spindle cells consistent with KS. Immunolabeling for HHV-8 stained the nuclei of the spindle cells (Figure 2).

An examination of serum samples for HIV by the ELISA method was negative and other tests revealed high titer of IgG antibodies to HHV-8. Computed tomography (CT) of the thorax and abdomen showed no visceral organ involvement. Azathioprine treatment was stopped. External radiotherapy was planned for the lesions on the leg and arm and face (Figure 1). The patient did not receive any chemotherapy. After two weeks of treatment, KS lesions completely regressed. Six months after radiotherapy and following withdrawal of immunosuppressive therapy, the patient had no evidence of any disease and a normal abdominal and thoracic CT scan.

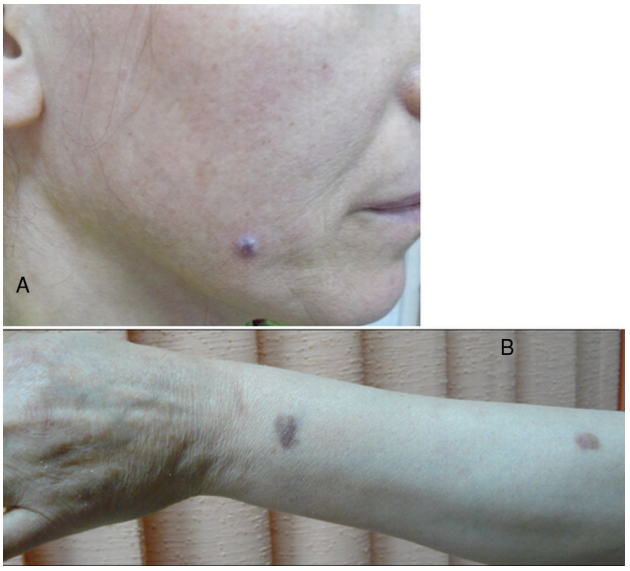

Figure 1. The lesion on the face (A) and left arm (B).

DISCUSSION

There are four clinical variants of KS: classic, endemic, AIDS-associated, and drug-related. Drug-related KS has been described in iatrogenic immu-

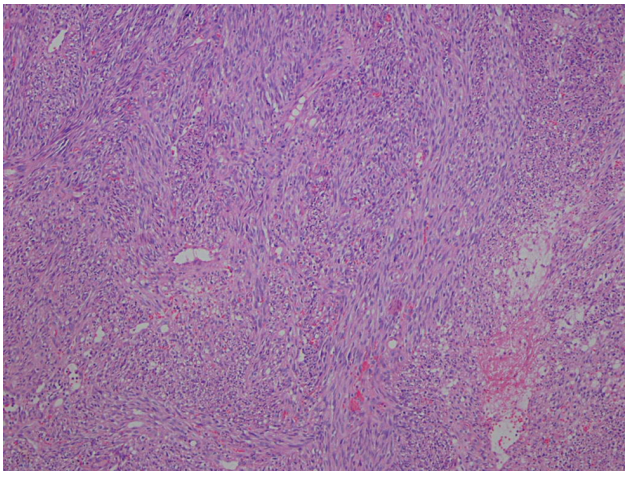

Figure 2. Proliferation of spindle cells, usually in a directional streaming pattern, mixed with endothelial cells, fibroblasts and inflammatory cells, and Kaposi's sarcoma strong immunopositivity for HHV-8.

nosuppressed organ transplant recipients and in a wide spectrum of patients receiving chronic immunosuppressive therapy. In patients with organ transplantation, the incidence of KS is markedly increased and estimated as 500- to 1000-fold greater than in the general population (8).

Ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract that affects the large bowel and is a major disorder under the broad group of inflammatory bowel diseases (IBDs). Current therapeutic strategies can be classified broadly based on disease activity into those that treat active disease (induction therapy) and those that prevent recurrence of disease once remission is achieved (maintenance therapy).

Of the various immunomodulatory agents, the most widely used are azathioprine and 6-mercaptopurine (6-MP). These two agents are purine analogs that interfere with nucleic acid metabolism and cell growth and exert cytotoxic effects on lymphoid cells. Four controlled studies have demonstrated the efficacy of azathioprine in the treatment of active UC (9-12).

From the efficacy standpoint, patients with steroid-dependent UC who are able to achieve remission with azathioprine and mesalamine and discontinue glucocorticoids can be maintained in remission with azathioprine alone (13).

In addition to the effect of immune suppression, however, there are specific characteristics of thiopurines that may promote carcinogenesis. Thiopurines work by incorporation of 'rogue' thiopurine nucleotides into DNA, but this subtly disrupts DNA structure (14), interferes with DNA replication and repair (14-16), creates unstable base pairs (17), and codes ambiguously, promoting mutagenesis (17).

Thiopurines also directly promote DNA damage by rendering it highly sensitive to radiation, particularly ultra-violet A (UVA) radiation, which accounts for 95% of UV radiation from sunlight. When thioguanine nucleotides are incorporated into DNA, the action of radiation creates reactive oxygen species, which attack both the DNA and its surrounding proteins, promoting mutagenesis (17-22). This is thought to account for the significant excess of non-melanoma skin cancer seen in those taking long-term thiopurines and the excess of brain tumors seen when leukemia treatment with MP was combined with cranial radiotherapy (23).

Recent work has demonstrated in vivo that individuals with IBD treated with thiopurines have higher rates of somatic mutations in circulating white cells than thiopurine-naive patients (24). The rate of mutation was proportional to both the dose and duration of treatment, and the pattern of mutations formed a specific thiopurine signature (24). Clinical data have linked the risk of malignancy during thiopurine treatment to the total dose of azathioprine received (25,26), thiopurine metabolite levels and TPMT mutations (27-30).

Nonetheless, the majority of patients placed on corticosteroids or immunosuppressive therapy do not develop KS, and considering the number of patients with UC disease requiring corticoids and/or immunosuppressive drugs, KS is an extremely rare complication. That has led many investigators to invoke a genetic or an ethnic predisposition in the development of this neoplasm because most cases of drug-related KS overlap with populations predisposed to classical KS. This rare neoplastic complication of IBD is most likely related to the immunosuppressive treatment. In light of the experience in transplanted patients who receive aggressive immunosuppression with several immunosuppressive drugs and in whom drug-related KS is relatively frequent, speculation suggests the combination of several immunosuppressive drugs increased the risk of KS in our patient. The optimal duration of maintenance therapy with azathioprine in patients with UC is currently unknown. In patients with Crohn's disease, the maintenance benefit of azathioprine or 6-MP can be observed for at least five years (31,32). Based on these data in Crohn's disease and the paucity of alternative maintenance therapies, in patients with UC in whom remission is maintained with azathioprine or 6-MP, treatment is generally continued indefinitely as long as there is no significant adverse side effect. Our patient had been taking azathioprine 100 mg per day for five years without any side effects.

Human herpesvirus (HHV)-8 is the main etiological agent of the four clinical-epidemiological forms of KS. That HHV-8 seems to be necessary but not sufficient to induce KS was noticed in transplant patients who were HHV-8-positive before transplantation, though the tumor occurred only on posttransplant immune suppression. HHV-8 is an important cofactor in the development of the disease in association with drug-related immunosuppression. Drug-related KS could be the result of viral reactivation by immunosuppressive drugs.

The clinical course of drug-related KS varies, depending on the degree of immune suppression. When immune suppression remains low, the symptoms are reminiscent of classical KS, with the lesions likely to resolve on suspension of treatment with the drug and with a latency period estimated at around one year. When the level of immune suppression is greater, symptoms are more aggressive—possibly even fulminant—and the latency period is shorter (33).

The natural history of cutaneous drug-related KS is not fully known. Both regression and cure of KS have been reported after withdrawal or reduction of immunosuppressive therapy (34).

There is no consensus on the optimal tumor-directed therapy for different classic KS manifestations. Because many active treatments have been described, therapeutic choices are often made based upon the experience and medical discipline of the treating clinician, but also include consideration of patient preferences and comorbid conditions. For patients who have limited volume disease causing symptoms (e.g., bleeding or chafing against clothes) or cosmetic disfigurement, we suggest local treatment rather than observation or systemic chemotherapy. The choice of modality (radiation therapy, excision, cryotherapy, laser ablation) depends on a number of factors, including the site and extent of the disease involvement as well as clinician and patient preference. In our patient, steroids and azathioprine were discontinued. After radiotherapy treatment, KS lesions completely regressed and the patient did not receive any chemotherapy. Six months after radiotherapy and following withdrawal of immunosuppressive therapy, the patient had no evidence of any disease and a normal abdominal and thoracic CT scan. The patient was started on 5-aminosalicylic acid (5-ASA, mesalamine) after the disappearance of KS.

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