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Case Report

Kaposi's sarcoma after T-cell costimulation blockade with abatacept in rheumatoid arthritis: a case report

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SUMMARY

What is known and objective: **Kaposi's sarcoma (KS) is a malignant neoplasm caused by HHV-8, a pathogen that leads to endothelial cell transformation when host defences are weakened.**
Case description: **Here we report the first case of KS during treatment with abatacept, a biologic agent targeting T-cell costimulation. The patient was a 64-year-old female with rheumatoid arthritis who developed multiple firm, purple-reddish nodules on the dorsal aspect of the right hand. Histological examination confirmed KS.**
What is new and conclusion: **Although a direct causal relationship between KS development and abatacept treatment cannot be proved, we hypothesize a role for costimulation blockade.**

WHAT IS KNOWN AND OBJECTIVE

Kaposi's sarcoma (KS) is a malignant angioproliferative neoplasm characterized by spindle-cell proliferation and a variable degree of lymphoplasmacytic infiltration.[1] The etiologic agent of KS is human herpesvirus-8 (HHV-8), a pathogen with high oncogenic potential, that leads to endothelial cell transformation under favourable conditions, in particular when host defences are profoundly weakened [i.e. acquired immune deficiency syndrome (AIDS) patients – epidemic or AIDS-related KS, or transplant recipients – iatrogenic KS]; however, individuals from endemic geographic areas (endemic KS) or sporadic patients (classic KS) can rarely develop this kind of cancer.[2] The geographic distribution of HHV-8 infection is strikingly variable among different regions, with high prevalence throughout Africa and the Middle East, moderate prevalence in the Mediterranean countries, and low prevalence in the United States and Northern Europe.[3] In Italy, a seropositivity of ~20% has been reported among the highest in Europe.[4] Complementary to virus exposure, a genetic predisposition has been suggested as contributing to the increased risk of KS in patients of Italian descent.[5]

Here we report a case of KS that developed during treatment with abatacept, a biologic agent approved for the treatment of rheumatoid arthritis (RA) that targets specific T-cell costimulation; the possible causal relation with abatacept exposure represents an emblematic example of the subtle equilibrium between HHV-8 infection and host response.

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CASE DESCRIPTION

The patient was a 64-year-old Caucasian female who came to our observation in 2013 because of an insidious onset of polyarthritis of the small joints of the hands and feet. Laboratory evaluation demonstrated a significant increase in acute-phase reactants and a positive result for rheumatoid factor but negative anti-citrullinated peptide antibodies (ACPA). According to the clinical picture and the radiographic evidence of metacarpophalangeal joints erosions, the patient satisfied the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria and was diagnosed with RA. The Disease Activity Score including 28 joints (DAS28) was 5·37 indicating a high disease activity. Therefore, treatment with subcutaneous methotrexate (20 mg/weekly), oral corticosteroids (prednisone 5 mg/daily) and on-demand non-steroidal anti-inflammatory drugs was started achieving a good disease control in few weeks.

In February 2016, she presented at a routine follow-up visit with a worsening disease activity (DAS28: 6·33). The patient was clinically eligible for biologic therapy and underwent pretreatment screening for latent tuberculosis infection (Mantoux skin test and chest radiography) and viral hepatitis serology as recommended by EULAR. Both results were negative. Abatacept was subsequently added to the previous treatment at the dose of 125 mg/week subcutaneously. After about 3 months of therapy, in June 2016, she presented at the follow-up visit with significant improvement in disease activity (DAS28: 3·63). However, in September 2016, the patient developed multiple firm, purple-reddish nodules on the dorsal aspect of the right hand and thumb (Fig. 1). After dermatological evaluation, KS was suspected and excisional biopsy of one of the lesions was performed. The histological examination revealed proliferation of irregular, slit-like vascular channels with flattened endothelium, spindle cells, and extravasated erythrocytes with a diffuse lymphoplasmacytic infiltrate (Fig. 2a,b). Immunohistochemistry (IHC) for CD34 showed strong cytoplasmic and membrane staining of the neoplastic cells confirming the vascular origin of the lesion (Fig. 2c), whereas staining for HHV-8 latency-

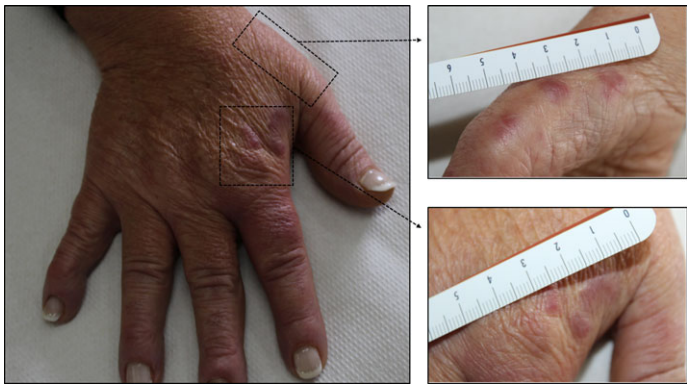

Fig. 1. Multiple firm, purple-reddish nodules on the dorsal aspect of the right hand and thumb. [Colour figure can be viewed at wileyonlinelibrary.com]

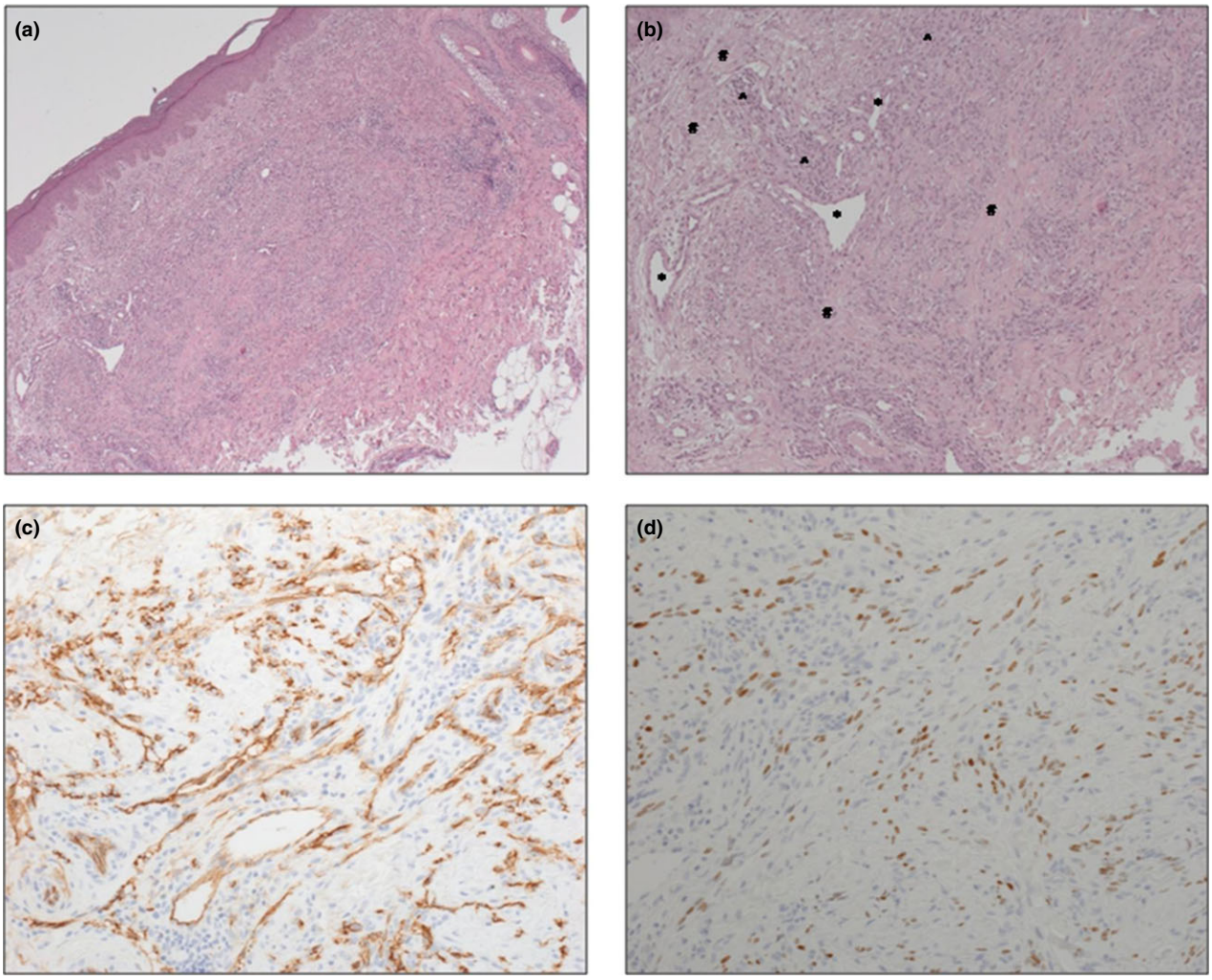

Fig. 2. Haematoxylin and eosin (H&E) staining at 5× magnification (a) and 10× magnification (b). Typical features of Kaposi's sarcoma are evident in reticular dermis, including proliferation of irregular, slit-like vascular channels with flattened endothelium (*), neoplastic spindle cells (#) and extravasated erythrocytes with diffuse lymphoplasmacytic infiltrate (^). Immunohistochemistry (IHC) at 10× magnification for CD34 (c) showing cytoplasmic and membrane staining of neoplastic cells. IHC at 10× magnification for HHV-8 LANA-1 (d) showing granular nuclear staining of neoplastic cells. [Colour figure can be viewed at wileyonlinelibrary.com]

associated nuclear antigen (LANA-1) showed a granular nuclear staining of neoplastic cells (Fig. 2d).

Kaposi's sarcoma was diagnosed, and treatment was immediately discontinued. The patient underwent extensive laboratory evaluation to exclude other potential causes of immunosuppression. White blood cell count was within the normal range, as were lymphocyte subsets differential count, total immunoglobulins and complement fractions C3 and C4. Human immunodeficiency virus serology was negative, whereas serum HHV-8 DNA was positive. No evidence of visceral or lymph nodal involvement was demonstrated by whole-body computed tomography (CT) scan. The patient was immediately sent to the oncologist for appropriate treatment.

WHAT IS NEW AND CONCLUSION

Although prevalent in immunocompromised hosts, KS has been rarely reported in patients with rheumatic diseases despite the extensive use of immunosuppressant medications.[6] In particular, to our knowledge, there has been no report of KS developed with abatacept treatment. Only a few cases have been reported in patients treated with anti-tumour necrosis factor alpha (TNF-α) agents.[7, 8] Anti-TNF-α medications, however, are the most widely used biologic medications worldwide, and therefore, they account for the largest number of KS reported during treatment with biologic medications in patients with RA. Abatacept is a soluble fusion protein which links the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) to the modified Fc portion of human immunoglobulin G1 (IgG1) and acts as a competitive inhibitor of T-cell costimulation delivered through the CD28-CD80/86 pathway. T cells are crucial for an optimal control of HHV-8 infection,[9] and their role is emphasized by the elevated incidence of KS in AIDS patients, also in those with a relatively conserved $CD4^+$ T-cells count.[10] HHV-8, in addition, has protective mechanisms against host T-cell and natural killer (NK) cell recognition, including a down-regulation of major histocompatibility complex class I and CD86 expression in infected cells, induced by the K5 viral protein.[11, 12] Also in *ex vivo* KS tumour cells, a loss of CD80/86 has been demonstrated[13]; concurrently, neoplastic cells fail to stimulate T-cell activation.[14] An elegant report by Barozzi *et al.* has demonstrated that changes in T-cell response in iatrogenic KS reflect the course of the disease better than changes in viral load.[15] Therefore, in the light of HHV-8's immunological escape strategy, we hypothesize in our case a mechanism in which iatrogenic costimulation blockade with abatacept is superimposed on HHV-8-induced CD80/86 down-regulation or complete knockdown. In this 'double-hit' fashion, the ability of HHV-8-infected cells to costimulate even minimally, specific T cells, is lost, thus opening the way for neoplastic transformation.

In conclusion, although a direct causal relationship between abatacept treatment and KS development cannot be proved in our case, the literature provides evidence of a complex interaction between HHV-8 and T lymphocytes. The increasing uses of T-cell-targeted therapies in RA demands attention on this potential risk. The possibility of KS in patients treated with abatacept who develop skin lesions should be investigated, especially in those from countries with higher HHV-8 seroprevalence and in populations with genetic vulnerability. In these patients, pretreatment screening for HHV-8 infection may be useful for minimizing the risk of KS.

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