

## AIDS-Related Kaposi's sarcoma and Associated Immune Reconstitution Inflammatory Syndrome

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### Abstract

Kaposi's sarcoma (KS) associated with AIDS (AIDS-KS) is the most prevalent neoplasia among patients with AIDS. Its incidence has decreased dramatically in recent years due to the widespread use of highly active antiretroviral therapy (HAART). Paradoxically, in relation to the introduction of HAART it may occur a worsening or development of AIDS-KS despite the improvement of the immune function. This unusual process is called immune reconstitution syndrome in Kaposi's sarcoma (IRIS-KS) and should not be confused with a failure of HAART. Early identification of AIDS-KS and previous or combined use of chemotherapy with HAART appears to be the most effective treatment to prevent the consequences of IRIS-SK.

**Keywords:** Immune reconstitution syndrome; Kaposi's sarcoma AIDS-associated; Highly active antiretroviral therapy; HIV

### Abbreviations

ACTG: AIDS Clinical Trials Group; AIDS: Acquired Immune Deficiency Syndrome; AIDS-KS: Kaposi's Sarcoma Associated to AIDS; G-CSF: Granulocyte Colony-Stimulating Factor; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; HHV8: Human Herpesvirus 8; IFN: Interferon; IL: Interleukin; IRIS-KS: Immune Reconstitution Inflammatory Syndrome Associated with AIDS-SK; KS: Kaposi's Sarcoma; LNA: Latent Nuclear Antigen; TAT protein: Transactivator of Transcription protein; TNF: Tumor Necrosis Factor; VEGF: Vascular Endothelial Growth Factor

### Introduction

Kaposi's sarcoma (KS) is a multifocal systemic tumor with origin in the endothelial cells which was first described by Moriz Kaposi in 1987. KS is classified into 4 variants: classic KS, endemic or African KS, iatrogenic KS and AIDS-associated KS (AIDS-KS). The AIDS-KS is the most prevalent form at present [1] and its first line therapy is the highly active antiretroviral therapy (HAART). This treatment usually produces a resolution of more than half of lesions but it is important to know that AIDS-KS can worsen by a paradoxical effect called IRIS-KS.

### Discussion

AIDS-KS is the most prevalent malignancy among patients with AIDS [2] and may be the first manifestation in these patients in 15% of the cases [1]. It is an AIDS-defining condition [2] and it occurs almost exclusively in men who have sex with men.

In its genesis are involved genetic, immune, endocrine and microbiological factors [1]. Chang et al identified in 1994 the human herpesvirus 8 (HHV8) as the causative agent of KS [2] but it seems insufficient to cause its development. Human immunodeficiency virus

(HIV) infection itself is thought to play a role in the growth of KS through the action of the transactivator of transcription (TAT) protein [3]. This protein contains amino acid sequences with homology to human angiogenic factors, although there is conflicting evidence as to whether or not TAT protein can directly activate HHV8 replication [3]. People infected by HIV have 20,000 times more risk of KS than the general population and 300 times more risk than other immunosuppressed individuals.

The majority of patients have only skin lesions [4] presenting as purpuric macules, patches and nodules and with multicentric and symmetrical distribution. In the AIDS-KS there is typically an early involvement of the face and diffuse distribution in the trunk. In case of visceral involvement, it is usually gastrointestinal and pulmonary.

The AIDS Clinical Trials Group (ACTG) Oncology Committee [5] reported the criteria for the evaluation of AIDS-KS. They are considered as high risk factors any of the following: edema or ulceration associated with tumor, widespread oral involvement, gastrointestinal KS or in other non-nodal viscera, CD4 <150/mm<sup>3</sup>, history of opportunistic infections, aphthae, B symptoms or Karnofsky score <70.

Patients with KS on HAART exhibit a less aggressive presentation compared with patients not receiving HAART [6] and there seems to be a clear relationship with the immune status (less than 15% of patients with AIDS-KS have more than 500 cells/μl) [1].

The diagnosis of AIDS-KS is based on the biopsy of lesional skin. Histology shows vascular channels lined by endothelial cells among a network of reticular fibers and extravasated erythrocytes with hemosiderin deposition. The identification and localization of HHV8 within KS lesional cells using latent nuclear antigen (LNA-1) is the most helpful immunostating technique available and it appears as stippled nuclear staining [2]. Patients with AIDS-KS should also receive a complete physical examination, a chest radiograph, a gastrointestinal endoscopy and a bronchoscopy or chest computed

tomography scan in case of digestive or respiratory symptoms respectively.

HAART regimen including a protease inhibitor represents the first-line treatment for the treatment of KS and it can be combined with different local therapies [6]. The effects of HAART on KS are multifactorial and include the inhibition of HIV replication, the improvement of the immune response against HHV8 and an antiangiogenic activity due to a decrease in the production of the TAT protein [6]. HAART with concomitant chemotherapy is indicated in visceral disease, rapidly progressive disease or widespread skin or oral involvement (>25 lesions) [6]. The first line chemotherapy is pegylated liposomal Doxorubicin (20 mg/m<sup>2</sup> intravenous every 2 weeks) or Daunorubicin citrate liposome (40 mg/m<sup>2</sup> intravenous every 2 weeks). Treatment with paclitaxel is restricted to patients with recurrent or refractory AIDS-KS after first-line chemotherapy [6]. Myelosuppression and infections are the major problem in patients treated with cytotoxic chemotherapy. The use of granulocyte colony-stimulating factor (G-CSF) is standard practice [6]. The average response time to HAART is 3 to 9 months [6]. HAART results in complete or partial resolution of KS lesions in 55-60% of patients with AIDS-KS [7] but there is a risk that an IRIS-KS occurs.

The IRIS-KS is an inflammatory process in which, paradoxically, there is a temporal association between the initiation of HAART, the improvement of the immune status and the onset or progression of AIDS-KS. Immune status improvement is evidenced by a decrease in the viral load and an increase in the CD4 cell count [8]. More than 100 cases of IRIS-KS have been described worldwide [9]. IRIS-KS incidence and mortality are higher in sub-Saharan Africa than in the United Kingdom [9] and it is a major contributor to KS-associated mortality in Africa [9]. It seems to be no differences in AIDS-KS body location between patients who develop IRIS-KS and those who do not.

The synergy between the humoral and cellular immune response against HHV8 secondary to HAART results in inflammation and tumorigenesis characterizing the clinical presentation of IRIS-SK [8]. Most AIDS-KS patients have undetectable or very low HHV8-specific cytotoxic T lymphocytes. After the initiation of HAART, CD8 T cells specific for HHV8 are detectable, and the recovery of this cell population is thought to be partly responsible for IRIS-KS [8]. In addition, HAART can increase the absolute number of lymphocytes secreting tumor necrosis factor alpha (TNF- $\alpha$ ), interferon gamma (INF- $\gamma$ ) and interleukin 1-beta (IL-1 $\beta$ ), which are related to the development of KS [8]. These inflammatory cytokines reactivate latent HHV8 and up-regulate the expression of integrins, matrix metalloproteases and vascular endothelial growth factor (VEGF). TAT protein encoded by HIV binds to integrin receptors on KS cells and promotes a mitogenic stimulus to VEGF [8]. Takahashi et al [10] speculated that PD-1 positive T cells are associated with IRIS. Previous reports showed that spindle cells of KS were CD31 (-) and D2-40 (+), whereas KS-IRIS cells were CD31 (+). These authors reported a case of KS-IRIS in which spindle cells showed strong staining for D2-40 but were weak for CD31. Therefore, they speculated that KS-IRIS is somewhat different from other forms of KS and therefore unique management strategies may be considered. Also, further studies on the mechanism of IRIS-SK are necessary as the response of HAART against HHV8 and AIDS-KS requires at least six months and, despite of this, the period of greatest risk of developing IRIS-SK is during the first 3 months of HAART [11].

It seems to exist an increased risk of SRI-SK in KS patients with lower median baseline CD4 [11,12], rapid increase in CD4 counts

during the initiation of HAART [13], high HIV viral load [8], associated edema [13], clinical pretreatment of KS, detectable plasma HHV8 DNA and hematocrit <30% [8]. The risk of IRIS-SK is similar among different antiretroviral drug regimens [11] although Bower et al [13] reported a higher risk in those patients performing both major HAART classes together, protease inhibitors and non-nucleoside reverse transcriptase inhibitors, in a single regimen.

The treatment of IRIS-KS with corticosteroids is not recommended because glucocorticoid treatment promotes HHV8 replication and tumor growth, worsening disease progression [8,14]. The regimen with HAART and chemotherapy demonstrate an effective suppression of HHV8 viral replication. HHV8 viral loads have been found to correlate with the extent of KS lesions, suggesting that the chemotherapeutic compounds could exert a direct antiproliferative effect on HHV8-infected cells, thereby limiting viral replication [15]. However, the number of chemotherapy cycles needed for IRIS-SK is still unclear [10].

In conclusion, it is important not to confuse IRIS-SK with HAART's failure and to know that IRIS-KS does not implicate a change in the antiretroviral therapy except in cases with potential irreversible damage [8]. Early identification of KS and chemotherapy treatment before or during HAART remain the most effective means for avoiding the serious consequences of IRIS-KS [8] and reducing its mortality [9,16].

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