Immunosuppression-associated soft-tissue tumours

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Abstract

Immunodeficiency and therapeutic immunosuppression inform the pathogenesis of certain soft tissue tumours, namely Kaposi sarcoma (KS) and Epstein–Barr virus (EBV)-associated smooth muscle tumours. KS comprises a group of clinical categories associated with local or systemic immunodysregulation: sporadic/classic KS, endemic (African) KS, epidemic (AIDS-related) KS, and iatrogenic (transplantation-associated) KS. Histologically, KS lesions progress from early (patch) stages, comprising networks of bland vascular proliferations, to later (plaque) stages, wherein spindle cells proliferate between vascular structures, and finally to the nodular (tumour) stage, which may show fascicles of intersecting spindle cells and PASD-positive hyaline globules. By immunohistochemistry, KS shows lymphovascular differentiation. EBV-associated smooth muscle tumours comprise a rare subset of smooth muscle tumours that typically occur in children with HIV/AIDS and adults following solid organ transplantation. They can occur in peripheral soft tissues, intracranially, or in visceral sites. Multiplicity is common and presumably a result of multiple infection events rather than metastasis from a primary site. Histologically, the differential diagnosis is limited to other smooth muscle tumours. These indolent tumours often persist despite therapy but rarely metastasize. Mortality usually results from the underlying disease process.

Keywords EBV; HHV8; HIV/AIDS; immunosuppression; Kaposi sarcoma; KSHV; smooth muscle; transplant; virus

Introduction

While the pathogenesis of most soft tissue tumours is still unknown, recognized etiopathologic factors include various physical and chemical agents, exposure to ionizing radiation, and inherited or acquired immunologic deficiencies. Determination of the exact cause is not always possible, given the long latency periods between exposure and disease and the cumulative effect of mixed environmental and hereditary factors. In cases of immunodeficiency and therapeutic immunosuppression, however, the inciting factor is often clearly documented, e.g. HIV/AIDS or post-transplantation immunosuppression, thereby facilitating clinical diagnosis. These immunologic deficits can be implicated in the development of certain soft tissue sarcomas, such as Kaposi sarcoma (KS) and Epstein–Barr virus (EBV)-associated smooth muscle tumours. It is worth noting that acquired regional immunodeficiency, or loss of regional immune surveillance, may also contribute to the development of angiosarcomas; this may occur in the setting of chronic lymphoedema, following radical mastectomy (Stewart–Treves syndrome), or with congenital or infectious conditions. These rare tumours resemble conventional angiosarcomas and lack a viral aetiology.

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Viruses are the putative cause of approximately 10–15% of all human cancers worldwide. When acting as oncogenic agents, viruses utilize a variety of mechanisms to transform human cells. Direct transformation occurs when viruses express viral oncogenes that directly transform infected cells. Viral oncoproteins reprogram host cells to favour viral production and induce genomic instability, which manifests with accumulation of point mutations and DNA damage. Viruses such as KS-associated herpesvirus (KSHV, also known as human herpesvirus 8 [HHV8]) and EBV can utilize direct transformation by encoding oncoproteins that inactivate two major regulators of the cell cycle, namely p53 and retinoblastoma (pRB) proteins. The tumour suppressor p53 induces cell cycle arrest or apoptosis in response to cellular damage and protects against genomic instability. In infected cells, inactivation of p53 leads to escalating genomic instability, loss of growth suppression and apoptotic function, and promotion of cellular transformation. The tumour suppressor pRB also regulates cellular apoptosis and loss or inactivation results in similarly deregulated growth. In addition to p53 and pRB, oncogenic viruses target many other molecules that regulate the cell cycle, leading to cellar transformation.

While the role of viral oncogenesis in the evolution of soft tissue sarcomas requires further investigation, there is a significant body of evidence to support the roles of KSHV and EBV in the pathogenesis of Kaposi sarcoma[1,2] and immunosuppression-associated smooth muscle tumours,[3,4] respectively.

KSHV (HHV8) and Kaposi sarcoma

First described in 1872, Kaposi sarcoma occurs in many forms, namely: i) sporadic or classic KS; ii) endemic KS, prevalent in sub-Saharan Africa; iii) epidemic, or AIDS-associated, KS; and iv) iatrogenic KS, following organ transplantation. In 1994, Chang et al. identified DNA fragments within KS tumour cells that were homologous to, but distinct from, capsid and tegument protein genes of the Gammaherpesvirinae, herpesvirus saimiri, and EBV.[1] This new human herpesvirus was designated KS-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV8), and has also been implicated in the development of primary effusion lymphoma and multicentric Castleman disease. Unlike other herpesviruses, KSHV prevalence shows a specific geographic distribution: more than half occur in sub-Saharan Africa, 20–30% occur in the Mediterranean, and less than 10% affect European or US populations. As KS is never observed in the absence of KSHV, the virus is considered the etiologic agent

for all forms of the disease. The marked variation in incidence of disease in various risk groups, however, suggests that while KSHV infection is necessary for development of KS, is it not sufficient. It is postulated that a variety of host factors, such as underlying disease state and immune status, influence transformation of infected cells.

KSHV infects various cell types, including B lymphocytes and endothelia, where it establishes latency. Reactivation, which is required for the development of KS, results in dysregulated immune responses and signalling pathways through propagation of viral genes. These genes are homologous to human cellular genes, including cyclins, apoptotic inhibitors, cytokines (e.g. VEGF), and receptors. KSHV also propagates a large multifunctional protein called latency-associated nuclear antigen 1 (LANA1), which interacts with p53, represses its transcriptional activity, and inhibits p53-induced cell death. HIV co-infection promotes tumour growth, as the virus induces various inflammatory cytokines and growth factors, as well as the HIV-1 Tat protein that stimulates KS cells to produce metalloproteinase that promotes tumour invasion and angiogenesis. This explains, in part, why AIDS-related KS is rapidly progressive and often fatal in the absence of timely antiretroviral therapy (ART).

While the four types of KS are clinically distinct, all relate to some form of immune dysregulation. Sporadic or classic KS typically occurs in older men in certain geographic regions (Russia, Poland, Italy, equatorial Africa), who often have a second malignancy or altered immune state. The prevalence of endemic (African) KS coincides with podoconiosis, a form of non-filarial elephantiasis that results from barefoot exposure to silica dust, resulting in localized immune suppression.[5] Epidemic (AIDS-associated) KS occurs in late stages of HIV infection, usually when CD4+ cell counts drop below 200 cells/mm3. Interestingly, iatrogenic (transplant-associated) KS occurs almost exclusively in renal transplant patients and is rarely seen in other solid organ transplant or bone marrow transplant patients. The disease develops months to years (average 16 months) after transplantation and the extent of disease directly correlates with loss of cellular immunity. Renal transplant patients receiving cyclosporine-based immunosuppression often show regression of KS lesions when the drug regimen is changed to rapamycin, which may have direct antitumour activity.[6]

All forms of KS present with similar pathologic features. The earliest (patch) stage (Figure 1) manifests with a flat lesion comprising a proliferation of small vessels surrounding larger ectatic vessels. There may be a loose ramifying network of irregular vessels, typically in the upper dermis. In contrast to angiosarcoma, the cells lining the vessels are bland and resemble normal capillary or lymphatic endothelia. Mononuclear inflammatory infiltrates are typically sparse. The more advanced (plaque) stage (Figure 2)produces an elevated lesion comprising a bland spindle cell component surrounding the proliferating vascular channels. As spindle cell foci expand, the monomorphic spindle cells form ill-defined fascicles separated by slit-like vessels containing erythrocytes. Nodular lesions (Figure 3) often show peripheral inflammatory cells, extravasated erythrocytes, hemosiderin deposition, and dilated vessels. Some tumours demonstrate characteristic intra- or extra- cellular periodic acid-Schiff-positive, diastase-resistant hyaline globules (Figure 4), which represent degenerated erythrocytes. While tumour cells

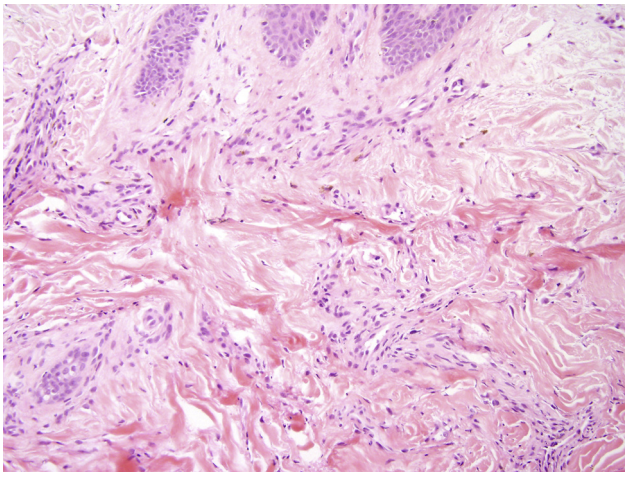

Figure 1 Patch stage, Kaposi sarcoma. This is a very subtle lesion, consisting of bland spindle cell proliferations adjacent to pre-existing small dermal vessels. Note the squamous epithelium at the top of the image.

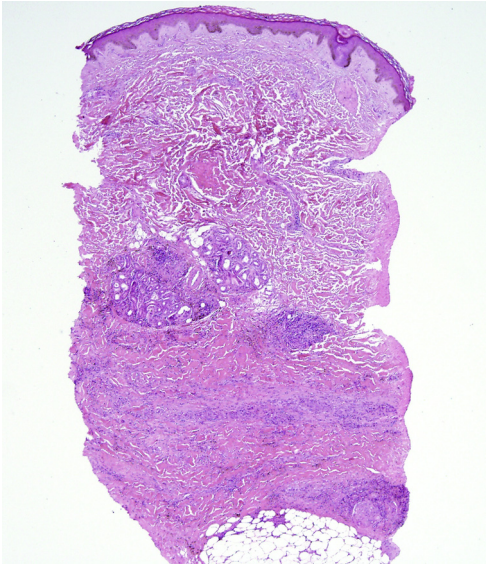

Figure 2 Plaque stage, Kaposi sarcoma. This punch biopsy shows an unequivocal spindle cell lesion proliferating in the deep dermis with minor extensions into subcutaneous adipose tissue.

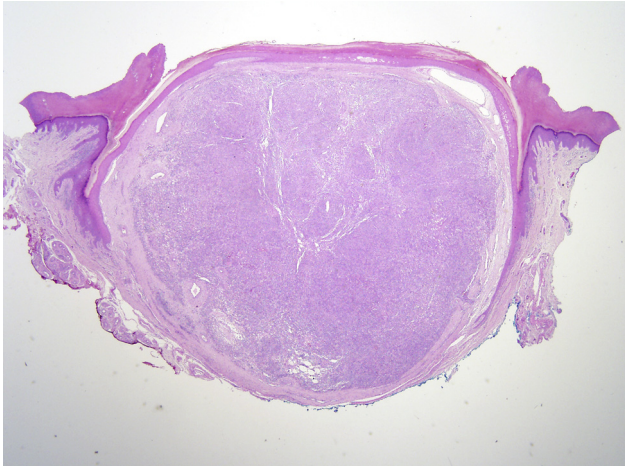

Figure 3 Nodular stage, Kaposi sarcoma. The lesion forms a well-developed spindle cell nodule.