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Mini-review

Role of environmental factors in the pathogenesis of classic and African-endemic Kaposi sarcoma

Thierry Simonart *

Department of Dermatology, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium

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Abstract

Kaposi sarcoma (KS) is a mesenchymal tumour associated with human herpesvirus-8 (HHV-8) infection. However, the incidence of HHV-8 infection is far higher than the prevalence of KS, suggesting that viral infection per se is not sufficient for the development of aggressive phenotype and that one or more additional cofactors are required. The great geographical variation in African-endemic and classic KS incidence points to a role for environmental factors in the etiology of Kaposi sarcoma. However, there are few unequivocably established environmental factors involved in KS pathogenesis. This review focuses on the environmental factors thought to be associated with KS, more particularly iron exposure and facilitation of transmission of HHV-8 infection by contact with blood-sucking arthropods.

Keywords: Human herpesvirus-8; Insects; Iron; Kaposi sarcoma; Soil

1. Introduction

Kaposi sarcoma (KS) is a mesenchymal tumour involving blood and lymphatic vessels. Different clinical and epidemiological settings have been identified: (1) Classic KS which usually follows a benign course and predominantly occurs in elderly men of Mediterranean or Eastern European Ashkenazi origin; (2) African-endemic KS, which usually involves the lower extremities and which existed for many decades before HIV in some equatorial countries of Africa; (3) immunosuppressive drug-related KS and (4) AIDS-associated KS. All these forms of KS share a similar histopathology characterised by the proliferation of spindle-shaped cells which are thought to represent the KS tumour cells, by neoangiogenesis, erythrocyte extravasation and by the presence of haemosiderin-laden macrophages and other inflammatory cells. Despite intensive research over the past 20 years, the pathogenesis of KS remains puzzling. KS spindle cells share features with smooth muscle cells, macrophages, dendritic cells and with endothelial cells of vascular or lymphatic origin, so that their precise origin remains controversial [1–4]. Most recent publications focused on the role of a recently identified human herpesvirus, named human herpesvirus-8 (HHV-8), which appears to be a necessary factor for KS development, irrespective of its epidemiological setting [5–7].

2. Transmission and role of HHV-8

The modes of transmission of HHV-8 are yet to be fully elucidated. In Europe and in the USA, sex may be an important route of transmission. The high incidence of HHV-8 antibodies in African children suggests the transmission from mother-to-child. The continuing

* Tel.: +32 2 555 46 12; fax: +32 2 555 49 69.
E-mail address: tsimonar@ulb.ac.be

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increase in the prevalence of HHV-8 infection throughout childhood points to transmission from child-to-child, via non-sexual routes (e.g. via saliva) in both Africa and southern Europe [8,9].

A large body of evidence indicates that HHV-8 has an important etiologic role in the four epidemiological forms of KS; (1) infection with HHV-8 precedes KS development [10]; (2) HHV-8 can be detected in all the epidemiological and histological forms of KS [11] and can directly infect the KS spindle cells [12]; (3) HHV-8 encodes several genes that can independently transform cells to a malignant phenotype [5]. However, HHV-8 infection appears as a very low risk factor for KS development. Most reports suggest a 2–10% global seroprevalence of HHV-8, with much higher rates in some areas [8,13,14]. Assuming a 5% prevalence of HHV-8 in the United States and a 1970s baseline incidence of KS in men in the United States of about 0.3 cases per 100,000 men, the HHV-8 rate would be one case of KS in every 17,000 HHV-8 infections [15]. In addition, seroprevalence rates in different geographic areas do not always correlate with KS development. For example, the HHV-8 seroprevalence is extremely high in the Ivory Coast, in Gambia, in Thailand whereas AIDS-related KS is rare and endemic KS is not known in these regions [16,17]. A similar finding among Brazilian-Amerindians has been published; seroprevalence was 53%, although KS has never been reported in this population [18].

In the years before human immunodeficiency virus (HIV) infection, the incidence of KS varied markedly across the African continent, and it was a disease primarily affecting men. In contrast, HHV-8 is prevalent in many African countries, including places where KS was almost unknown before HIV, and it is as common in women as in men [19] Therefore, the geographical distribution of KS in Africa before the spread of HIV and its predominance as a disease affecting men are not a simple reflection of the distribution of HHV-8 and point to the role of environmental factors in the development of the tumor. There are few unequivocably established environmental factors involved in KS pathogenesis. Nevertheless, environmental etiologies may explain much of the international variation in KS risk and possibly differences among racial/ethnic groups.

3. Geographical distribution of African-endemic KS and classic KS

Before the HIV epidemic, KS was an endemic tumor in Africa with a greater geographic variation in incidence than any other cancer, representing up to 9% of all cancers in men in certain parts of Sub-Saharan Africa [20]. The highest prevalence of endemic KS in Africa lies in a broad strip running from the Uganda, Sudan, and Democratic Republic of Congo border southwards through Rwanda and Burundi. In the Northeastern provinces of the Democratic Republic of Congo, and in Rwanda and Burundi, KS accounts for up to 17% of adult male malignancies [21,22]. Prevalence diminishes rapidly away from this endemic region. In addition, narrow belts of high incidence stretched westward from eastern Zaire to the Coast in Cameroon and southward down the Rift Valley into Malawi [20] In these regions, both high altitude and relatively high rainfall were associated with increased incidence of African KS [21,23].

The incidence rates of classic KS in European population-based registries are also markedly variable. Low rates were reported in England, Wales and Denmark [24,25]; intermediate rates were reported in Sweden, France and Spain [26], whereas higher rates were reported in Italy, Greece, Iceland and the Faroe Islands [27–29]. The highest incidence rates in Europe were reported in two Mediterranean Italian islands: Sardinia (24.3 per million in men and 7.7 per million in women between 1977 and 1991) [30] and Sicily (30.1 per million in men and 5.5 per million in women between 1976 and 1984) [27].

4. Genetic pre-disposition

The occurrence of classic KS in men of Mediterranean or Eastern European Ashkenazi descent suggested a possible genetic pre-disposition to this tumor. In 1983, early in the AIDS epidemic, the HLA-DR5 genotype was reported to be associated with the occurrence of KS in homosexual men from New York City [31]. Subsequent studies have however failed to confirm such an association in either AIDS-related or endemic KS [32–34].

Although a higher incidence of classic KS is reported to occur in Jewish and Mediterranean populations, it is not clear whether this pattern reflects geographic or ethnic characteristics. A study performed in Los Angeles indeed indicated the highest incidence rate of classic KS in Jews born in Eastern European and Mediterranean countries [35]. Second-generation American Jews were at lower risk than their immigrant parents [35], suggesting that differences in HHV-8 transmission or environmental factors are preponderant.