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Debate

Iron: a target for the management of Kaposi's sarcoma?
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Abstract

Background: Kaposi's sarcoma (KS) is a mesenchymal tumour associated with human herpesvirus-8 infection. However, the incidence of human herpesvirus-8 infection is far higher than the prevalence of KS, suggesting that viral infection *per se* is not sufficient for the development of malignancy and that one or more additional cofactors are required.

Discussion: Epidemiological data suggest that iron may be one of the cofactors involved in the pathogenesis of KS. Iron is a well-known carcinogen and may favour KS growth through several pathways. Based on the apoptotic and antiproliferative effect of iron chelation on KS cells, it is suggested that iron withdrawal strategies could be developed for the management of KS. Studies using potent iron chelators in suitable KS animal models are critical to evaluate whether iron deprivation may be a useful anti-KS strategy.

Summary: It is suggested that iron may be one of non-viral co-factors involved of KS pathogenesis and that iron withdrawal strategies might interfere with tumour growth in patients with KS.

Background

Kaposi's sarcoma (KS) is a mesenchymal tumour that has been identified in different clinical/epidemiological settings: classic KS, an indolent form usually found in elderly men of Mediterranean or Eastern European origin; African-endemic KS, which usually involves the lower extremities (figure 1) and which existed well before the HIV epidemic in some equatorial countries of Africa; immunosuppressive drug-related KS; AIDS-associated KS and HIV-negative gay-related KS. All these forms of KS share a similar histopathology characterised by the proliferation of spindle-shaped cells, by neoangiogenesis, by erythrocyte extravasation and by the presence of haemosiderin-laden macrophages and other inflammatory cells.

A large body of evidence indicates that human herpesvirus-8 (HHV-8) has an important etiologic role in the pathogenesis of KS; 1) HHV-8 can be detected in all the epidemiological and histological forms of KS [1-3] and can directly infect the KS spindle cells [4,5]; 2) HHV-8 encodes several genes that can independently transform cells to a malignant phenotype [6]; 3) infection precedes development of the tumour and tracks tightly with KS risk [3]. However, HHV-8 infection appears as a very low risk factor for KS development. Most reports suggest a 2 to 10% global seroprevalence of HHV-8, with much higher rates in some areas [7,8]. 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 100000 men, the HHV-8 rate would be one case of KS in every 17000 HHV-8 infections [9]. In addition, seroprevalence rates in different geographic areas do not always correlate with KS development. Eighty-nine percent to 100% of serum samples from the general population in non-KS-endemic African areas such as Gambia or the Ivory Coast, proved to be positive; such a rate is higher

Figure 1
Aggressive African-endemic KS of the foot.

than the 40% rate found in sub-Saharan Africa, where KS is endemic [10]. A similar finding among Brazilian-Amerindians has been published; seroprevalence was 53%, although KS has never been reported in this population [11]. Another puzzling finding is the similarity of rates of HHV-8 infection among men and women in Africa [10]. Since the KS found in Africa is about 8 to 10 times as common among men as among women, there must be some reason other than HHV-8 infection to explain this difference.

Thus, there is now compelling evidence that HHV-8 is a necessary, albeit not sufficient, cause of KS and that one or more additional cofactors are required. These co-factors may represent a target for the prevention and/or treatment of KS.

Discussion
High incidence of KS in iron oxide-rich volcanic clays
Endemic KS in Africa predated the HIV epidemic and showed evidence of geographic restriction [12,13], suggesting a genetic or an environmental cofactor. 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 [13,14]. Prevalence diminishes rapidly away from this endemic region. Amazingly, these areas of high prevalence of endemic KS are characterised by a common geologic substratum, composed of iron oxide-rich volcanic clays (figure 2). This observation led Dr. Ziegler to suggest that chronic exposure to volcanic clays plays a role in the pathogenesis of African-endemic KS [14]. His intriguing hypothesis was that ultrafine particles of clay penetrate the skin of the feet during barefoot walking, leading to dermal lymphatic damage and to impaired local immunity. Further data have strengthened the hypothesis of soil exposure and percutaneous penetration of ferromagnetic particles as a risk factor for KS. More particularly, barefoot walking, time spent in contact with water and exposure to wet soils appear as important risk factors for KS in Uganda [15,16]. In water, a clay emulsion disaggregates into particles less than 2 μm, a size that can readily enter sweat glands of the feet [17]. While cultivating (especially in the rainy season when clay soils are pliant and workable), soil particles might thus enter the sweat glands and pores of the feet, perhaps aided by micro-abrasions caused by the high quartzite content of these soils. In this perspective, we have reported the case of a metallurgist with classic KS involving his palm. Iron filings were detected in the underlying cutaneous tissues by magnetic resonance imaging, supporting the hypothesis that percutaneous penetration of iron may favour the development of KS [18].

Exposure to volcanic clays may also help to explain the distribution of classic KS in the Mediterranean, prevalent in volcanic regions such as the Pelopenese, Sardinia and Sicily. Supporting this hypothesis, Montella et al. noted that the risk of classic KS was twofold higher among people born near Mount Vesuvius than among people born in neighbouring areas [19]. Interestingly, a magmatic substrate similar to that of the East African Rift system (extrusive igneous rocks composed of mafic (and hence iron oxide-rich) minerals) [20] is also present in Iceland and in the Faroe Islands which are other geographic areas known to exhibit surprisingly high incidence rates of classic KS [21]. One of the characteristics of these mafic minerals is that they are highly weatherable, allowing a significant release of iron compounds in the environment, such as in water or in vegetables [22]. The unusually high prevalence of the classic and endemic forms of KS in regions of intercontinental rifts and volcanism may thus point to prolonged exposure to indigenous iron oxide-rich volcanic soils as a common aetiological risk factor.

Carcinogenic role of iron
Several observations have been made linking cellular iron content to the development of cancers [23]. In prospective studies in animals, administration of excessive amounts of injected or oral iron increases markedly the risk of adenocarcinomas, colorectal tumours, hepatomas, mammary tumours, mesotheliomas, renal tubular cell carcinomas, and sarcomas [23]. In humans, injections of iron complexes have been observed to result in sarcomas at the sites of deposition [24]. Similarly, inhalation of industrial sources of iron may be responsible for respiratory tract neoplasias [25,26]. Patients with hemochromatosis, a genetic disease characterised by increased iron absorption, show a markedly enhanced susceptibility to primary liver cancer and various other malignancies [27]. Patients with moderate elevation of body iron levels may also have an increased risk of neoplasms of various kinds [28,29].

The pathogenic role of iron in cancer development and/or progression is not fully understood. Several carcinogenic pathways have schematically been described: (a) iron is an essential element for dividing cells, because it is incorporated in numerous enzymes that play a role in DNA replication and cellular metabolism. More particularly, iron can directly promote the growth of some cancer cells [30], probably through its role in the activation of ribonucleotide reductase, a key-enzyme in DNA synthesis, responsible for the reduction of ribonucleotides to deoxyribonucleotides [31]; (b) iron may promote the formation of mutagenic hydroxyl radicals [23]; (c) iron excess diminishes host defences through inhibition of the
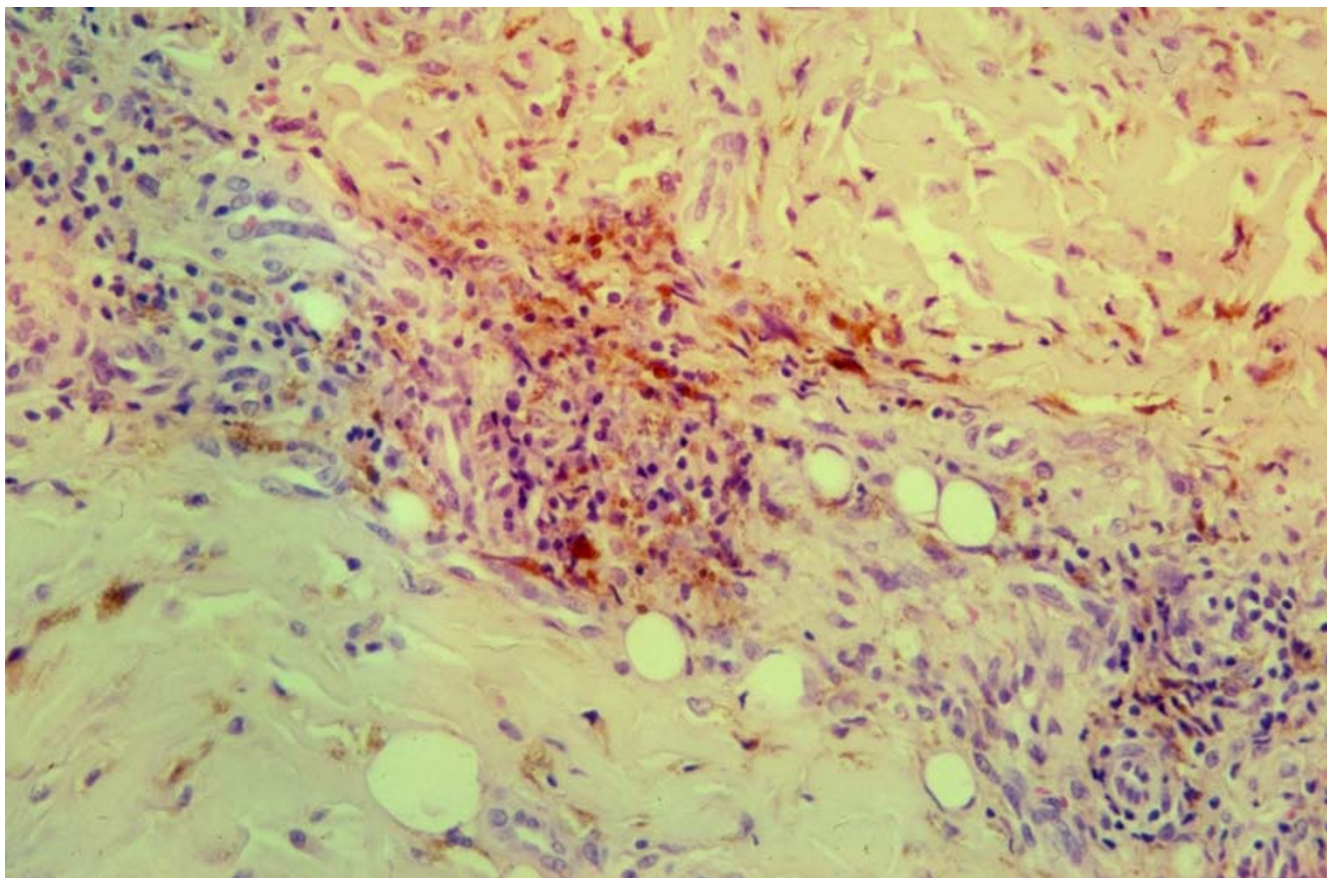
Figure 2
Landscape in the Kigali area (Rwanda): the red-brown colour of the soil is related to an intense weathering of the minerals of the geological substratum with massive release of fine particles of iron oxides and iron hydroxides.

activity of CD4 lymphocytes and through the suppression of the tumoricidal action of macrophages [23]; (d) iron can enhance host cell production of viral nucleic acids [32] which may be involved in the development of some human cancers. Other data support more specifically a direct role of iron in the pathogenesis of KS: 1) the addition of iron salts to KS-derived cells can stimulate their growth [33]; 2) iron can induce the expression of anti-apoptotic signals in human dermal microvascular endothelial cells [34], which may alter the homeostasis of microvessels and promote neo-angiogenesis. Interestingly, one of the histological hallmark of KS is the presence of ferritin granules and the presence of haemosiderin-laden macrophages (figure 3). Even at the early 'patch-stage' of KS development, red blood cell extravasation and the presence of siderophages are encountered, providing a possible continuous source of iron for endothelial and KS cells.

Iron status in individuals prone to develop KS
Amazingly, a high iron load is expected to be found in the different epidemiological forms of KS. Iron load is ele-

vated in renal transplant recipients who had received blood transfusions for years before the availability of erythropoietin and before transplantation. Iron load could also be higher in patients with episodes of haemo-lytic anaemia which are common features in Central Africa or in Mediterranean areas, mostly secondary to glu-cose-6-phosphatase deficiency, thalassemia or sickle cell anaemia. In HIV infection, the alteration of iron metabo-lism has been recognised in a variety of ways [32]. The majority of patients in advanced stages of AIDS are hypo-ferrimic and moderately hyperferritinemic, and they have increased deposition of iron-ferritin and/or haemosiderin in cells of the bone marrow, brain white matter, skeletal muscle, and sometimes in the liver. The 'iron hypothesis' may also provide a non-hormonal explanation for the lower prevalence of KS among women, as they are known to have lower iron reserves than men. In this connection, it may also help to understand the reported disappearance of KS lesions during or just after pregnancy [35]. It is inter-esting to note that there are high incidence rates of KS among Bantu in the South African Transvaal [36] and that these individuals are known to frequently suffer from iron

Figure 3
'Plaque-stage' KS showing the presence of numerous haemosiderin-laden macrophages.

overload resulting from the interaction between their genotype and an environmental factor – namely, increased amounts of bioavailable iron in the diet. The source of this dietary iron is a traditional fermented beer that is home-brewed from local crops in steel drums [37].

Iron withdrawal strategies: a role for the management of KS?
Based on a possible role of iron in tumour development, several studies have shown that iron withdrawal strategies possess considerable activity *in vitro* in inhibiting tumour growth [38,39]. More particularly, we found that the chemically unrelated iron chelators desferrioxamine (DFO) and deferiprone could inhibit the growth and induce the apoptosis of human KS-derived cells at clinically achievable concentrations [40], suggesting that iron chelation may represent an experimental therapeutic approach for the treatment of KS. Iron chelators have also been shown to inhibit vascular cell adhesion molecule-1 (VCAM-1) expression in human dermal microvascular

cells [41]. As VCAM-1 may favour angiogenesis and account for inflammation-augmented tumour development [42,43] and as it is used by cancer cells to enhance metastatic implantation and spread [42], VCAM-1 inhibition represents another mechanism through which iron chelation might prevent KS growth.

We previously initiated studies investigating the effect of DFO on the growth of immortalized KS-Y1 cells in immunodeficient mice, which resulted in paradoxical enhancement of the growth of the xenografts [44]. These results could be related to the upregulation of angiogenic growth factors by DFO [45] as well as to its short half-life in mouse plasma [46] and to its subsequent inability to induce significant iron depletion in non-iron-overloaded mice [44]. Another disadvantage of DFO is its poor ability to permeate cell membranes and bind intracellular Fe pools [47]. Obviously, investigation of iron chelators showing higher iron chelation and use of animal models closely mimicking human KS are required.

Several chelators with greater antiproliferative and/or better pharmacokinetics than DFO have been recently developed [47]. Among the most promising molecules are the 2-pyridoxal isonicotinyl hydrazone (PIH) analogues [39]. Their antiproliferative activity is much greater than that of DFO and is comparable to that of bleomycin and cisplatin [48]. These molecules affect the expression of several molecules involved in cell cycle through their ability to chelate intracellular iron [39]. As PIH analogues may have potential as agents to treat cancer, they represent potential drugs for KS therapy. Another promising chelator with greater efficacy than DFO is ICL670A [49], which is an orally active representative of a new class of tridentate iron chelator developed for the treatment iron overload and which has been shown to be relatively well-tolerated in phase III studies [50]. Triapine, a ribonucelotide reductase inhibitor, has completed phase I studies in patients with advanced leukaemia and with advanced solid tumours [51,52] and is currently in phase II clinical trial as an anticancer agent. CP502, GT56-252, NaHBED, and MPB0201 are examples of other new chelators in preclinical/clinical development [53].

Models closely mimicking human KS are obviously required to evaluate the effect of potential anti-KS drugs. Although there is currently no animal model that accurately represents KS pathogenesis, a number of mouse models have been established that attempt to address specific factors known to contribute to the development of the disease. In early studies, transformed KS cell lines such as KS Y-1 were injected into nude mice, which led to the development of KS-like lesions. This model was used to investigate the effect of various therapies on KS growth, such as human chorionic gonadotropin or interleukin-4 [35,54]. However, these xenografts models may be flawed, because none of the KS cells used for tumour establishment harbour HHV-8 sequences, as opposed to human KS lesions. More promising models have recently been obtained by creating transgenic mice expressing the HHV8-encoded chemokine receptor (viral G protein-coupled receptor) within hematopoietic cells [55]. The mice develop angioproliferative lesions in multiple organs that morphologically resemble KS lesions. These lesions are characterized by a spectrum of changes ranging from erythematous maculae to vascular tumours, by the presence of spindle and inflammatory cells, and by expression of vGPCR, CD34, and vascular endothelial growth factor [55]. In another model, HHV-8 was injected into normal human skin transplanted onto SCID mice. Injection of HHV-8 induced lesion formation that is morphologically and phenotypically consistent with KS, including the presence of angiogenesis and spindle-shaped cells latently infected with HHV-8 [56]. This in vivo system has the advantage of using human skin cells as the target of the virus, and may be the most accurate model of KS; however, it does not completely mimic KS and is difficult to reproduce [57].

Summary

At present, several types of iron withdrawal strategies have been shown to possess considerable activity *in vitro* in inhibiting tumour growth. Based on the probable role of iron in KS pathogenesis, it is suggested that manipulations of iron load might interfere with tumour growth in patients with KS. However, further studies using potent iron chelators in suitable KS animal models are critical to evaluate whether iron deprivation may be a useful anti-KS strategy.

Lists of abbreviations

DFO: desferrioxamine

HHV-8: human herpesvirus-8

KS: Kaposi's sarcoma

VCAM-1: vascular cell adhesion molecule-1

Competing interests

None declared.

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