Kaposi’s sarcoma and the new herpesvirus

The Austro-Hungarian dermatologist, Moritz Kaposi, first described Kaposi’s sarcoma (KS) over 100 years ago [1] as a rare, slowly progressive tumour of elderly males with lesions mainly confined to the skin of the extremities. It later emerged that a more aggressive KS was endemic in central Africa. In developed countries, KS is now most commonly associated with HIV infection, and is characterised by widely distributed lesions, visceral as well as lymph node involvement and a rapidly progressive course. It also occurs iatrogenically in immunosuppressed individuals.

The clinical presentation of KS is unusual. Often, multifocal lesions arise de novo in distributions inconsistent with metastatic spread. New lesions contain multiple cell types which form slit-like vascular spaces lined by flattened endothelial cells. A cellular infiltrate of lymphocytes and plasma cells is often present. Later lesions are dominated by more uniform spindle-like cells. Several growth factors are produced by the different cell types present in KS lesions in vivo and in vitro and may be required for their growth [2, 3]. Cultures established from KS tumours may induce ‘KS-like’ lesions of murine origin when injected into nude mice [4], showing that some of the released growth factors can induce the development of such lesions. These observations, together with reports of regression of KS lesions in transplant patients after withdrawal of immunosuppressive medication, suggest that early KS, at least, is not truly malignant.

However, the monoclonal nature of individual KS nodules [5] and the fact that ‘malignant’ cell lines (tetraploid karyotype, growth as human tumour in nude mice) can be established from biopsies [6] suggests the possible transformation of some cells to a malignant phenotype. The origin of KS spindle cells is still controversial. Vascular or lymphatic endothelium, cells from venous lymphatic junctions, fibroblasts, smooth muscle cells and dermal dendrocytes have all been proposed as possible progenitors.

The rarity of KS in patients with haemophilia in contrast to homosexual men with HIV infection, and its geographic distribution suggest a sexually acquired infective cause [7]. In 1994, DNA of a previously unknown herpesvirus was discovered in KS lesions, but not in unaffected tissue from the same patient [8]. The two fragments of herpes viral DNA obtained had a high degree of homology with herpesvirus saimiri, an oncogenic herpesvirus which can cause T-cell lymphomas in New World monkeys, and with Epstein–Barr virus [8]. The complete genomic sequence has recently been published [9].

Several lines of evidence suggest that this virus, currently called Kaposi, sarcoma-associated herpes virus, or human herpesvirus 8 (HHV8), causes KS. HHV8 DNA has been found in all variants of KS [10–13], and is found in c. 50% of blood samples from patients with the disease [14], but not from healthy blood donors. In asymptomatic HIV-infected patients, detection of HHV8 in peripheral blood mononuclear cells predicts the subsequent development of KS lesions [14, 15]. Although HHV8 is rarely detected in saliva or sputum of KS patients, detection of the virus in broncho-alveolar lavage fluid from AIDS patients is predictive of the presence of pulmonary KS [16]. HHV8 can be found in semen samples from HIV-infected gay men, but the reported frequency varies [17–19]. The virus has also been reported in semen samples from healthy donors by some [18, 19], but not all [17] groups. It is also present in many cases of multicentric Castleman’s disease [20], a rare syndrome consisting of angiofollicular hyperplasia, adenopathy and fever, which is statistically associated with KS. As these different reports illustrate, the extent to which HHV8 is present in the general population is still controversial.

Antibodies to a latent nuclear antigen can be detected by immunofluorescence in an HHV8 positive B-cell line [21–23]. Antibodies to a recombinant capsid-related antigen have been detected by ELISA and Western blot [24]. Both are present in 80–90% of patients with Kaposi’s sarcoma and in c. 30% of homosexual men infected with HIV. However, antibodies to these antigens are seen in <5% of patients with haemophilia or intravenous drug users, whether infected with HIV or not. Over 30% of HIV-negative African controls are antibody positive [22]. Antibodies to a set of undefined structural antigens have been found in 20% of blood donors in the USA [25]. Thus, the prevalence of HHV8 in the different HIV risk groups matches that expected for the postulated transmissible KS agent [7]. In Western countries it seems to be sexually transmitted and its epidemiology...
may resemble that of HSV-2 [23–25]. Geographic differences in HHV8 prevalence suggest that other modes of transmission may prevail in some African countries.

In AIDS patients, HHV8 has been consistently detected in the rare body cavity-related lymphoma [26] and occasionally in other B-cell lymphomas. Many of these lymphomas have also been positive for Epstein–Barr virus.

How HHV8 might contribute to the development of KS lesions is not yet known. One of the open reading frames codes for a protein that is a homologue of human D cyclins and it is possible that infected cells proliferate through a cyclin-dependent mechanism [27, 28]. The HHV8 cyclin homologue can promote phosphorylation of the retinoblastoma protein and interacts with cdk6 [28]. A similar cyclin homologue is present in the herpesvirus saimiri genome, although it is not identical with the transforming genes, which are located at the opposite end of the genome. HHV8 also encodes an interleukin-6 homologue, which is expressed in infected B-cells, but not in KS lesions [29]. Other possibly transforming proteins encoded by HHV8 include: the chemokine homologues, MIP-1 and MIP-2; an interferon regulatory factor; and homologues of bcl-2, a G-protein coupled receptor and neural adhesion molecule [9, 29]. Besides these, HHV8 has other genes with no obvious homology which may mediate as yet unknown transforming mechanisms [9, 28, 29].

By in-situ PCR, HHV8 can be shown to infect both the spindle cells typical of advanced KS and the atypical flat endothelial cells lining vascular spaces of early KS lesions [30]. The virus establishes a latent infection consistent with a transforming role, and some genes that have the potential to interfere with the cell cycle or intracellular signalling (e.g., cyclin homologue, G-protein coupled receptor homologue) are expressed [27]. Thus, HHV8 may contribute to cell proliferation. Cell cultures established from KS lesions, including those capable of inducing the growth of ‘KS-like’ lesions in nude mice, often do not contain detectable HHV8 or lose it after a few passages [31].

Other factors besides HHV8 infection may contribute to the development of KS. Immunosuppression is an important cofactor and probably allows HHV8 to replicate to high levels [14]. Experimental evidence suggests that the tat protein of HIV-1 may co-operate with a fibroblast growth factor to enhance KS cell proliferation [32]. The emergence of KS-like lesions in mice transgenic for HIV-1 tat has also been reported [33]. However, the role of tat in AIDS patients with KS has not been fully resolved. Hormonal co-factors have been proposed but their role in vivo awaits further corroborate [34].

While epidemiological findings, in particular the distribution of antibodies to HHV8 and its constant presence in KS lesions, support the role of this virus in the pathogenesis of KS, its precise role in the development of the lesions remains to be elucidated.

H. D. L. BRLEY and T. F. SCHULTZ
Department of Medical Microbiology and Genitourinary Medicine,
University of Liverpool,
Duncan Building, Daulby Street,
Liverpool L69 3GA

References