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Classic Kaposi's Sarcoma and Vascular Endothelial Growth Factor

Sir,

Kaposi's sarcoma (KS) is a highly invasive and intensely angiogenic neoplasm of unknown cellular origin. Angiogenesis and capillary permeability can play a central role in the development and progression of KS. The principal features of KS are abnormal vascularization and the proliferation of endothelial cells and spindle cells. KS cells appear to be of smooth muscle origin but secrete a potent inducer of endothelial cell chemotaxis and invasiveness which could be responsible for angiogenesis and the resulting highly vascularized lesions. This inducer could be vascular endothelial growth factor (VEGF). VEGF has been reported to be a predominant angiogenic factor expressed in KS cells (1), although basic-fibroblast growth factor (bFGF) also acts synergistically with VEGF in the induction of angiogenic KS-like lesions in a mouse model *in vivo* (2).

Data *in vitro* support the hypothesis that abnormal vascularization in the KS lesions may be, at least in part, the result of the secretion of VEGF. Here we report, for the first time, *in vivo*, an increased amount (3- and 2.5-fold, respectively) of VEGF in sera of 2 patients with classic KS, as compared with 5 control sera from age and sex-matched healthy subjects (95 ± 33 pg/ml). VEGF levels were determined in duplicate using a commercial enzyme-linked immunosorbent assay (R&D Systems, Abingdon, United Kingdom). The level of VEGF was calculated using a standard curve obtained with human recombinant VEGF (from 7.8 to 1000 pg/ml).

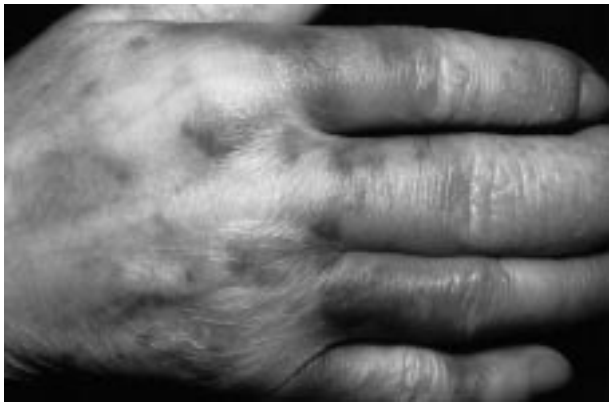

Fig. 1. Red-purple macules and plaques on the hand, patient 1.

CASE REPORTS

Case 1

A 77-year-old Spanish man, without any significant personal or family history, had asymptomatic cutaneous lesions in the form of reddish-blue plaques on the legs which gradually enlarged over the previous 2 years. He reported that they had gradually increased in number and size, extending to other areas of the body. He did not receive any specific treatment. Physical examination revealed macules, plaques and red-purple nodules on his hands, left wrist, forearms, abdomen, feet and legs (Fig. 1). The lymphoedema of his hands and forearms were so severe as to hinder function. Complete blood cell count and blood chemistry were normal. HIV test was negative. A biopsy specimen from the left foot confirmed the diagnosis of KS. A computed tomographic scan of the thorax and abdomen showed no visceral extension of KS. Serum VEGF was 316 ± 45 pg/ml. Treatment with interferon-α2b was started. The patient did not come to follow-up and continued the same treatment in another centre.

Case 2

A 72-year-old Spanish man presented in 1996 with a 1-year history of purplish plaques and nodules, starting on the toe of the left foot and gradually spreading to involve the left leg. Medical history included non-insulin dependent diabetes. HIV test was negative. A diagnosis of classic KS was confirmed by a biopsy specimen from the foot. Endoscopy and colonoscopy were normal. Abdominal images from computed tomography scan and X-ray examination of the chest were normal. Results of a complete blood cell count and serum chemistry

studies were unremarkable. Serum VEGF was 240 ± 36 pg/ml. In 1998, worsening lymphoedema and stasis changes of the right leg were present. Examination revealed multiple violaceous plaques and nodules on the left leg and foot. He had also several discrete violaceous nodules and macules on the fingers and dorsum of the right hand. Treatment with interferon-α2b was indicated.

DISCUSSION

There have been diverse opinions as to whether KS represents a reactive vascular proliferation or a true neoplastic proliferation. There is increasing epidemiological evidence that suggest the involvement of an infectious agent in the origin of KS. Recently, a new human herpesvirus has been implicated as a possible aetiological candidate for all variants of KS (3), and it has been suggested that G-protein-coupled receptor of KS-associated herpesvirus is a viral oncogene and angiogenesis activator (4).

KS cells have been shown to produce angiogenic growth factors and cytokines such as bFGF, TNF-α, IL-1, IL-6, VEGF and oncostatin M, and to express high-affinity receptors for several cytokines (5). VEGF is the most potent angiogenic factor identified to date and it also acts as a vascular permeability factor. VEGF stimulates the endothelial cells lining nearby microvessels to proliferate and to migrate (6). As a potent permeability factor, VEGF promotes extravasation of plasma fibrinogen, leading to fibrin deposition which alters the extracellular matrix (7). Over-expression of VEGF is observed in many epithelial tumours, in psoriatic skin, in UVB-radiation-induced erythema, in delayed hypersensitivity skin reactions and in bullous diseases such as erythema multiforme and bullous pemphigoid (8).

VEGF appears to be the major cytokine responsible for maintaining the long-term growth of KS cells in culture, suggesting an important role for this cytokine in the pathogenesis of KS. It has been shown that KS cells express higher levels of VEGF than both human umbilical vein endothelial cells or human aortic smooth muscle cells, and also express high levels of *Flt-1* and KDR, the receptors to VEGF (9). VEGF antisense oligonucleotides specifically block VEGF mRNA and protein production and inhibit KS cell growth in a dose-dependent manner (9). Western blot and enzyme-linked immunosorbent assay analysis of cell culture supernatants demonstrated that the VEGF protein is secreted by stimulated KS spindle cells in sufficiently high amounts to activate proliferation of human dermal microvascular endothelial cells (10). Also, analysis of primary human AIDS–KS lesions revealed that high amounts of VEGF mRNA and protein were present in KS spindle cells *in vivo* (10).

In summary, we report here for the first time that classic KS patients have increased levels of VEGF in serum, which can theoretically favour the progression of the disease. We speculate that future therapies for KS might include angiogenesis inhibitors capable of either directly inhibiting both growth factors and cytokines or blocking their receptors.

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