In Spain, syphilis rates in adulthood increased by about 75% between 1999 and 2004; the total number of cases was 675 per 100 000 inhabitants in 1999 and 1156 in 2004. Cases of congenital syphilis have increased 700%, rising from 2 in 1999 to 16 in 2004, with 9 cases reported in 2000, 8 in 2001, 15 in 2002, and 4 in 2003.

In 2004 the number of reports has continued to climb, with 12 cases described in the province of Malaga alone.[3] In 2005, cases of neurosyphilis in Madrid[4] and malignant syphilis in Galicia[5] and Madrid[6] have been published. The latest study on an epidemiologic outbreak was conducted in Las Palmas de Gran Canaria, in the Canary Islands.[7]

Because of the recent rise of syphilis in Europe, closer control consisting of early screening and treatment of affected pregnant women is necessary, since neonatal syphilis can be prevented through education programs focused on sexually transmitted diseases and good prenatal care (compulsory Venereal Disease Research Laboratory screening in pregnant women).[8]

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Classic Kaposi Sarcoma Associated With Lymphedema Following Arterial Catheterization

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To the Editor:

Classic Kaposi sarcoma (CKS) is a vascular neoproliferation typically seen on the lower limbs of elderly patients. The condition is associated with human herpes virus 8 (HHV8); however, its high prevalence in Mediterranean countries suggests that other environmental factors may be relevant in its etiology.

We describe a 59-year-old man with asymptomatic violaceous plaques and nodules present from 1 year earlier on the right leg (Figure 1). The lymphedema observed had been present since a femoral artery catheterization performed 6 years earlier for intestinal bleeding. The histologic study of the lesion showed vascular proliferation of fusiform cells with erythrocytes dissecting the collagen bundles, consistent with Kaposi sarcoma (KS). The immunohistochemical study was positive for HHV8. Contrast-enhanced magnetic resonance angiography showed no vascular abnormalities or arteriovenous fistulas in the lower limbs. Ten cycles of liposomal doxorubicin of 20 mg/m^2/3 wk were administered, and complete clinical remission was achieved (Figure 2).

The classic variant of KS is characterized by violaceous papules or

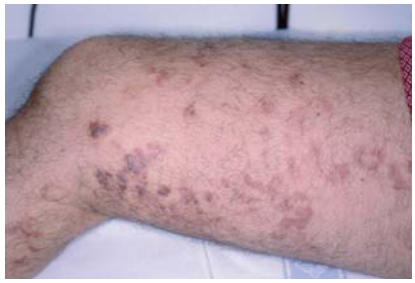

Figure 1. Onset of violaceous papules and nodules. Note the edema of the affected limb.

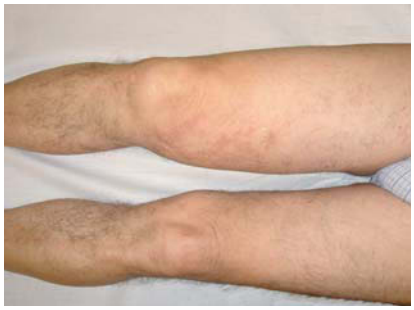

Figure 2. Clinical appearance of the lesions after treatment.

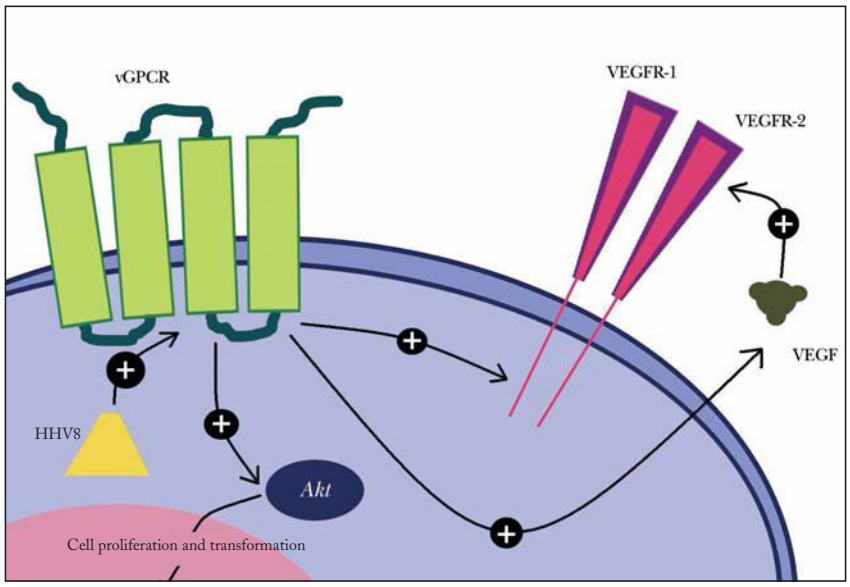

Figure 3. Molecular mechanisms of action in human herpes virus 8 (HHV8) in cell conversion and in the secretion of angiogenic factors and receptors. VEGFR-1 indicates vascular endothelial growth factor receptor 1; VEGFR-2, vascular endothelial growth factor receptor 2; vGPCR, viral G-protein-coupled receptor.

nodules in the distal part of the limbs of older men, with a slow course. It appears that HHV8 is a necessary factor: regardless of the tumor variant, more than 95% of neoplastic cells are infected with this virus.[1] This virus is responsible for coding proteins similar to human oncoproteins that modify the cell cycle and proliferation, apoptosis, angiogenesis, and T-helper cell-mediated immune response.[1] Viral oncoproteins are tumor promoters that induce the synthesis of angiogenic molecules, such as the viral G-protein-coupled receptor (vGPCR),[1,2] vascular endothelial growth factor (VEGF),[2,3] and the expression of kinase insert domain-containing receptor (KDR).[2] vGPCR is a "pirated" human cytokine receptor that promotes the appearance of KS: it regulates cell proliferation and transformation through the Akt molecule, as well as angiogenic factors such as VEGF and its type 1 and 2 receptors.[2] vGPCR triggers endothelial intracellular and/or autocrine proliferation, and induces tumor development in nearby cells either by direct contact or paracrine secretion[2] (Figure 3). Loss of cell proliferation control and an alteration of the immune response and cytokine pathways favor the development of KS. Other factors, such as immune disorders,[1] abnormal lymphatic drainage,[4,5] vascular oncogenesis,[6] and the trans-activating (tat) protein of human immunodeficiency virus (HIV) are also implicated in the etiology and aggressiveness of CKS.

In the case presented, the tumor site, limited to the lymphedema, suggests an etiologic relationship with the circulatory disorder. The magnetic resonance angiography ruled out arteriovenous fistulas due to the catheterization as an explanation of the appearance of KS-like lesions (pseudo-KS, Bluefarb-Stewart syndrome). The absence of vascular abnormalities, the histologic appearance of the lesions, the positive immunohistochemistry reactions for HHV8, and negative HIV serology results supported a diagnosis of CKS.

Lymphedema is common before or during the onset of KS,[1,4,5,7,8] and could be an early lesion in the spectrum of KS.[8] Lymphographic study of patients with CKS reveals structural and functional drainage abnormalities consistent with those of primary or secondary lymph vessels.[4] Lymphatic stasis causes local cellular immune dysfunction,[7] lymphocyte traffic, and increased Langerhans cells[5,9] and stimulates lymphangiogenesis[7] and angiogenesis,[7,9] thus favoring the appearance of benign and malignant vascular neoplasms.[7] KS cases have been described in areas of lymphedema,[5,8] venous thrombosis,[3] complicated catheterization,[6] venipuncture,[10] abscesses,[10] and trauma.[10] Physical stimuli would increase the secretion of vascular growth factors (basic fibroblast growth factor) and inflammatory mediators (interleukin 1β, interleukin 6, and tumor necrosis factor α) that promote vascular proliferation and the acquisition of fusiform cell characteristics of KS in normal endothelium.[1,6]

Abnormal vascular drainage would promote autocrine secretion of VEGF and its receptor (KDR),[3] promoting the proliferation of endothelial cells infected with HHV8. An increase in VEGF that stimulates angiogenesis has been described in both thrombosis and lymphedema.[3]

The appearance of KS in areas affected by circulatory disorders and lymph vessels without arteriovenous fistulas supports the pathogenic role of local immune abnormalities and the secretion of vascular growth factors such as VEGF. Viral oncoproteins act on this factor, as well as on other angiogenic agents, and play a role in KS genesis that is increasingly more apparent. The Köebner phenomenon and the secondary secretion of angiogenic molecules could explain the appearance of KS in areas affected by trauma caused by invasive tests. In patients most susceptible to KS, such as those infected with HIV, invasive procedures pose a risk for this neoplasm. In conclusion, it appears that lymphatic stasis can lead to vascular neoplasms such as CKS via physical and immunologic mechanisms, as well as by secretion of angiogenic agents.

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