

Case Report

Classic Kaposi's sarcoma: multiple bluish red papules in an old man's foot

典型卡波希肉瘤：老年男性患者足部的多發性紫色丘疹

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An 84-year-old Chinese male patient presented with multifocal bluish red papules on the right foot. Skin biopsy showed a nodular vasoformative tumour composing of spindle cells with slit-like spaces. Human herpesvirus (HHV-8) immunostaining was positive. Based on the clinical features, histopathology and HHV-8 staining, the diagnosis of classic Kaposi's sarcoma was made. Response to radiotherapy was satisfactory.

一名 84 歲中國男患者右足呈多個紫色丘疹。皮膚活檢顯示一個由梭形細胞及空隙形成的血管性結節腫塊。8 型人類疱疹病毒 (HHV-8) 免疫染色法檢驗呈陽性。經臨床表現，組織病理學及免疫染色法檢驗確診為卡波希肉瘤。對放射治療反應良好。

Keywords: Classic Kaposi's sarcoma, human herpesvirus 8, Kaposi's sarcoma associated herpesvirus

關鍵詞：典型卡波希肉瘤，8 型人類疱疹病毒 (HHV-8)，波希肉瘤關聯疱疹病毒

Introduction

Kaposi's sarcoma (KS) is a multicentric vascular proliferation with four epidemiological variants.

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They are classic KS, African-endemic KS, AIDS-related epidemic KS, and iatrogenic immunosuppression-associated KS. The four variants share identical histologic features but develop in specific populations with different sites of involvement and rates of progression. Among these variants, classic KS is primarily a rare skin disorder of the lower limbs affecting predominantly elderly men. The following is a case report of classic KS.

Case report

An 84-year-old Chinese male patient presented with asymptomatic bluish red papules over the right foot for twelve months. The lesions increased

in number and extent gradually. The patient was a social drinker who quit smoking for 34 years, with no ongoing medications including steroid and immunosuppressants, and denied any past history of sexually transmitted disease. He enjoyed good past health except history of an operation for benign intestinal tumour in 1991 and left herniorrhaphy in 1995.

Physical examination showed multiple purple-blue to red confluent papules and nodules over the medial, lateral and posterior aspects of the right foot (Figure 1). The differential diagnoses included KS, angiosarcoma, lymphangio-sarcoma and bacillary angiomatosis.

Investigations including biochemistry and complete blood picture were unremarkable. HIV antibody was negative. A skin biopsy of a lesion showed a nodular vasoformative tumour composing of spindle cells with slit-like spaces and occasional vacuoles containing red cells. The cells exhibited mild cytologic atypia with brisk mitosis. HHV-8 immunostaining was also positive (Figures 2-5). The clinical and histological features were compatible with classic KS. The patient received radiotherapy with regression of lesions.

Discussion

Kaposi's sarcoma is an angioproliferative disease characterised by inflammatory cell infiltration, intense and aberrant angiogenesis, oedema, and growth of spindle cells of endothelial or monocytic cell origin (KS cells).

Our patient was an 84-year-old local Chinese. The lesions were localised on his right foot. His negative HIV serology and absence of immunosuppressive intake are features compatible with classic KS. Classic KS most commonly affects elderly males of Mediterranean, Eastern European or Jewish descent. The male to female ratio was 2.3:1 and the median age of



Figure 1. Multiple purple-blue to red confluent papules and nodules over the right foot.

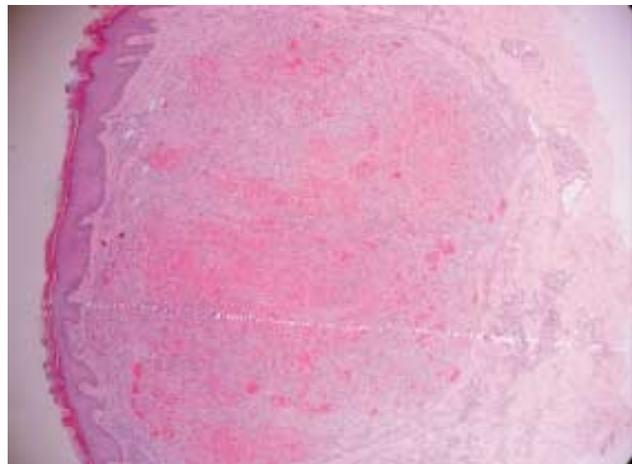


Figure 2. Nodular proliferation of spindle cells in the dermis. (H&E, original magnification x 4).

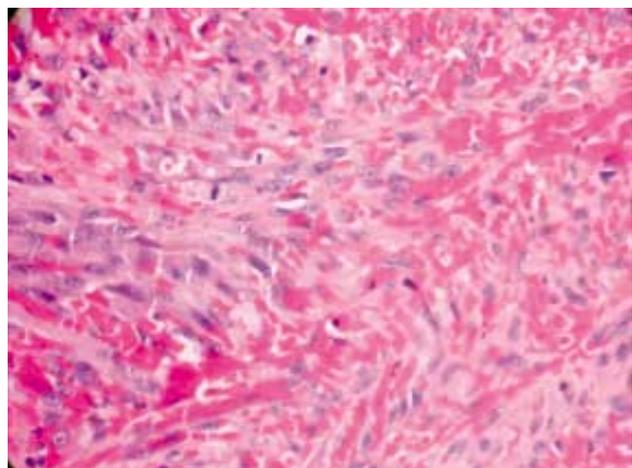


Figure 3. Spindle cells with minimal atypia forming slit-like spaces and containing red blood cells. Mitotic figures are brisk. (H&E, original magnification x 40).

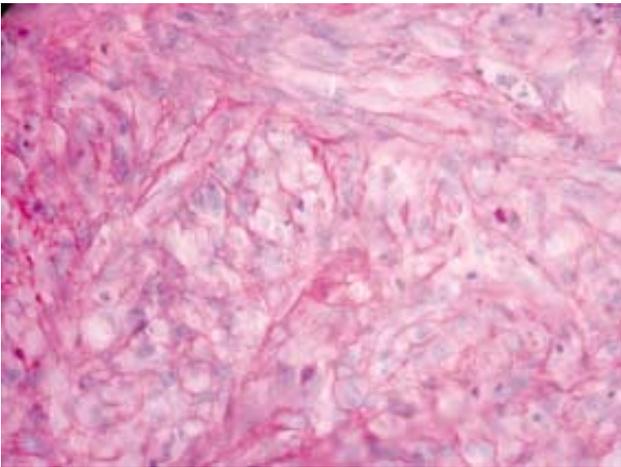


Figure 4. PAS-positive globules present both extra and intracellularly. (Periodic Acid-Schiff stain. Original magnification x 40).

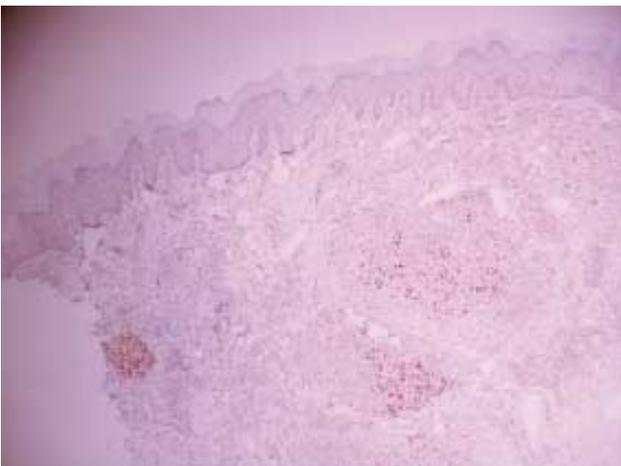


Figure 5. HHV-8 immunostain shows positive nuclear stain in some of the spindle cells. (Original magnification x 40).

onset was 65 years (range, 20-92 years) in a study of 248 consecutive patients with classic KS in Israel.¹ There are only few reports of classic KS in Hong Kong Chinese. Our case and all the patients described in a local report originated from southern China.²

Classic KS most often begins as ecchymotic-like painless macules on distal lower limbs. These lesions progress slowly and many lesions merge

into large plaques. Some lesions occasionally evolve into nodules and tumours. Unilateral involvement is generally found at the onset of KS. Later on, the lesions spread centripetally and might be found bilaterally and multi-focally. In our case, the lesions involved the right lower limb only with multifocal purple-blue confluent papules and nodules over the foot.

The tissue specimen of the patient was found to stain positive for human herpesvirus 8 (HHV-8). In 1994, Chang et al identified two small fragments of a novel Herpes virus genome in KS tissues, KS330Bam and KS631Bam.³ The virus was known as Kaposi's sarcoma-associated herpesvirus, also designated human herpesvirus 8 (HHV-8), a large double-stranded DNA virus. Epidemiological and experimental studies established a strong link between HHV-8 and KS. HHV-8 infection precedes development of KS and HHV-8 DNA can be detected from KS tissue in different clinical stages of the disease.⁴ In patients with multifocal and visceral involvement, semiquantitative analysis showed that HHV-8 DNA load was higher in comparison with those with localised disease. In patients with the nodular stage, a higher viral load was found in contrast to the patch and plaque stages. This showed a correlation between viral load and disease severity.⁵

HHV-8 infection is infrequent. The prevalence is about 1% to 5% in North America and Northern Europe, approximately 40% in men who had sex with men and 5% to 20% in Mediterranean populations.⁶ HHV-8 can be transmitted sexually, particularly through male homosexual contact. It is associated with the number of homosexual partners and it correlates with a history of sexually transmitted diseases.⁷ However, the risk factors in heterosexual people are less clear. Additional modes of transmission of KSHV included horizontal mother-to-child transmission and transmission via saliva.⁸ Other as yet unknown routes of transmission are possible.

The HHV-8 genome contains genes that help the virus to survive and replicate in the host. Normally, a balance exists between growth activators or suppressors in cells. An upset of this balance consequent to the inhibition of growth suppressors and the addition of growth activators in HHV-8 infected cells leads to cell transformation.⁹ The growth suppressors included p53 and retinoblastoma gene products and the growth activators included viral transcription factors, viral proto-oncogenes, and inhibitors of apoptosis and viral cytokines. The HHV-8 chemokines skew the cellular environment towards a Th2 profile and KS lesions predominately contain Th2 type lymphocytes. A local inhibitory effect of Th2 cytokines on the development of an anti-viral Th1 response along with antagonistic activity on chemokine receptors expressed by leukocytes could provide a survival mechanism for HHV-8.¹⁰

The course of classic KS is slowly progressive. In a study of 248 consecutive patients with classic KS in Israel,¹ it was found that only 1.6% (n=4) died of classic KS. The median follow-up period in the study was 20 months (range, 1-360 months). 39% had any progression (any local or diffuse spread of lesions, as well as evidence of any development requiring initiation or change in treatment such as bleeding or pain), the median time to progression was 15.4 months. Dissemination of disease was found in 18% who were eligible for this analysis and the median time was 22.4 months. The occurrence of visceral spread was small which was found in 4% of the 202 eligible patients. Secondary malignancies were not rare, however, 19% had second malignancies, most frequently occurring were adenocarcinomas and lymphoreticular disorders. In our case, the lesions were confined to the leg only.

There is no cure for KS. The major goal of treatment is palliative, i.e. to reduce morbidity by

shrinking cutaneous and oral lesions and to prevent disease progression. For minimal cutaneous KS, options include local treatment with cryotherapy, intralesional therapy, e.g. vinblastine, radiation therapy, topical cis-retinoic acid (alitretinoin), low-dose chemotherapy or interferon-alpha. Observation alone which was adopted in 31 % of patients in a study was found to be not an unfavourable factor for the outcome of classic KS.¹ For patients with systemic KS, extensive cutaneous disease, resistant disease and tumour associated lymphoedema, the primary treatment is systemic chemotherapy. The older therapeutic agents included doxorubicin and bleomycin. The newer ones are liposomal formulation of the anthracyclines and paclitaxel. Liposomal anthracyclines such as liposomal doxorubicin and liposomal daunorubicin, are currently considered the initial chemotherapeutic agents of choice for extensive KS. As KS is a systemic disease, local surgical excision is reserved for single problematic cutaneous lesions in patients who refuse other systemic or local treatments.¹¹ Our patient had limited disease and had marked response to radiotherapy alone. Nowadays, there are novel approaches to interfere more directly with the pathogenesis of KS, in particular, AIDS-related KS. Investigational therapies include anti-angiogenesis compounds, cytokine inhibitors, signal transduction inhibitors and anti-HHV-8 agents. They are, however, considered experimental and used only in clinical trial settings.¹¹

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