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Parotid mass as an early sign of Kaposi's sarcoma associated with human herpesvirus 8 infection

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Abstract
Kaposi's sarcoma of an intraparotid lymph node is extremely rare in non-immunocompromised human immuno-1 deficiency virus (HIV)-negative patients. We report a case of a left parotid mass as an early sign of Kaposi's sarcoma-associated human herpesvirus 8 (HHV-8) infection in a 57-year-old patient. After subtotal parotidectomy and histopathological diagnosis of lymph node localization of Kaposi's sarcoma, an accurate dermatological investigation revealed a solitary small lesion in the left foot. Chemotherapy with five cycles of vincristine gave a temporary response of the cutaneous lesion. Seven months later, a few small, firm, purplish-red lesions appeared in different areas of the body, but no adjuvant treatment was accepted by the patient since the lesions occasionally disappeared or remained stable in size. At four years follow-up, there has been no recurrence in the parotid region, and the patient is alive with cutaneous disease but in good general health. The problems related to the diagnosis, the management strategy of such a rare condition and the prognosis are also discussed.

Key words: Herpesvirus; Kaposi Sarcoma – Associated; Parotid Gland

Introduction

Kaposi's sarcoma (KS) is a malignant tumour histologically composed of spindle cells that form and surround irregular slit-like vascular channels and spaces.[1] First recognized in 1872 by Moriz Kaposi,[2] who termed it 'idiopathic multiple-pigmented sarcoma of the skin', KS prevalently occurs in four distinct clinical forms: sporadic, endemic, transplantation-associated and acquired immunodeficiency syndrome (AIDS)-related. The sporadic form is primarily a skin disease that is found around the ankle and on the leg. Sporadic KS prevalently affects elderly men of Mediterranean, East European or Jewish heritage. The course of the disease is generally indolent, and the patients survive an average of 10–15 years before dying of other causes. The endemic form is found in African adult males and also children (lymphadenopathic variant), where it can account for up to nine per cent of all malignant tumours.[3] Extracutaneous involvement in the endemic form is usually associated with an extremely poor prognosis. The transplantation-associated form is found among organ transplant recipients; it usually shows a fatal course, but spontaneous regression may be observed if immunosuppression is removed. The HIV-related form is generally seen in the later stages of infection with HIV, particularly among homosexual men.

The term idiopathic was probably adopted by Moriz Kaposi to emphasize the unknown aetiology of the lesion, the aetiopathogenesis of which remained unclear until the close relationship between (HHV-8) and KS was demonstrated.[4,5]

Involvement of the salivary glands in all the four clinical forms, especially in HIV-associated patients, has been previously reported in the literature,[6–10] but an intraparotid lymph node in a non-immunocompromised and HIV-negative patient is extremely rare. To the best of our knowledge, only three cases of primary KS of an intraparotid lymph node not correlated to immunodeficiency have been reported in the literature,[11–13] and there are no reported cases in which the involvement of an isolated intraparotid lymph node by KS associated with HHV-8 infection was found as an early sign of the disease. Furthermore, primary involvement of the parotid gland parenchyma is extremely rare, with five HIV-related cases so far reported in the literature.[14]

We present a rare case of a left parotid mass as an early sign of a HHV-8 associated cutaneous KS in an HIV-negative patient. The problems related to the diagnosis, management strategy and prognosis of such a condition are also discussed.

Case report

A 57-year-old Caucasian male presented in February 1996 with a 2 × 2 cm non-tender, movable and painless swelling of the left parotid gland of four-months duration. On anamnestic examination, a history of a long stay in Africa as a teacher was reported. Further anamnesis was negative for drug abuse, blood transfusions, transplantation or previous diagnosis of HIV infection. Physical examination did not show any change in colour of the overlying skin. Computed tomography of the left parotid region showed a solid, heterogenous mass with a diameter of about 2 cm

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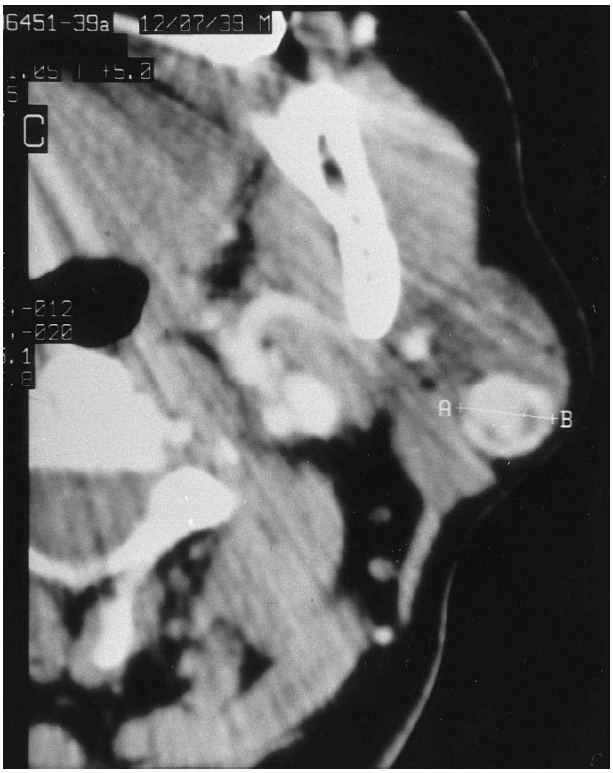

FIG. 1

Axial contrast-enhanced CT scan shows an oval-shaped, high-density mass on the left parotid gland.

and well-defined borders within the superficial lobe of the gland (Figure 1). On admission, the patient's general status was excellent. Further ENT examination revealed no other abnormalities. The patient had a history of ischaemic heart disease that had caused an asymptomatic myocardial infarction, for which he had undergone an aorto-coronary bypass operation in 1991.

At the time of parotid surgery, routine laboratory data, chest X-ray and electrocardiogram were all unremarkable. The patient had no detectable humoral or cell-mediated immune defect. Fine needle aspiration cytology of the mass was not performed. A left subtotal parotidectomy revealed a reddish oval mass measuring 2 cm in diameter in the inferior part of the superficial lobe of the gland without macroscopic evidence of infiltrative spread of the neoplasm in the surrounding parenchyma. Pathologic examination of an intra-operative frozen section of the specimen showed a lymph node localization of KS, which was confirmed by the definitive histological diagnosis. As a result, the patient underwent a more extensive assessment for general disease. Dermatological evaluation revealed a solitary 0.5×0.5 cm blue-red papule on the external side of the left foot. Histological examination after excisional biopsy was indicative of cutaneous KS. Chest and abdominal CT were negative for visceral and other lymph nodal lesions. Anti-HIV antibodies were shown to be negative in three evaluations performed by the EIA method every six months. Serum positivity for anti-HHV8 antibodies was tested by the ELISA method.

Treatment with five cycles of vincristine was delivered; therapy with interferon had to be avoided because of the patient's heart condition. Four years after treatment, the patient was alive and in good general health, without any radiographical evidence of the KS lesion in visceral organs, but with multiple small cutaneous lesions in several sites of the body.

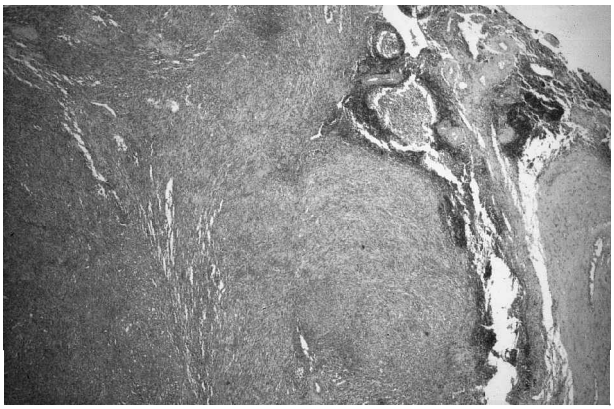

FIG. 2

Low magnification of the intraparotid lymph node showing almost total replacement of spindle cell proliferation of KS enclosing frequent slit-like vascular spaces (H & E; × 25).

Histopathologic and molecular findings

The specimen consisted mainly of salivary gland parenchyma. A lymph node with severely altered architecture was found in the gland. It was histologically characterized by a proliferation of spindle cells with large monomorphic hyperchromatic nuclei and many eosinophilic inclusions. Spindle cells were arranged in coils, or were fence-like, and a vascular component was very commonly represented (Figure 2). Mitoses were abundant. An infiltration of lymphocytes, plasma cells and macrophages (CD68-positive) containing haemosiderin, as well as many extravasated erythrocytes, were seen among the spindle cells.

Immunohistochemical examination of the spindle cell component showed positivity for vimentin and CD34 antigen (Figure 3) and negativity for cytokeratins, smooth muscle actin, α-muscle actin, HMB 45 and S-100 protein. The residual lymph node parenchyma was marked by CD45. The diagnosis was definitively KS of an intraparotid lymph node, without extracapsular spread.

To determine the presence of the HHV8 genome in the lesions, polymerase chain reaction amplification was performed using a set of primers specific for the KS330 Bam_{233} fragment, as previously described.[14] A clear positivity for a band of 233 bp was present in the DNA extracted from the lymph node and salivary gland. The band was isolated and cloned using the TOPO™ TA Cloning kit (Invitrogen Corporation, Carlsbad, CA-USA) and sequenced using the ThermoSequenase fluorescent labelled kit (Amersham Pharmacia Biotech, Uppsala,

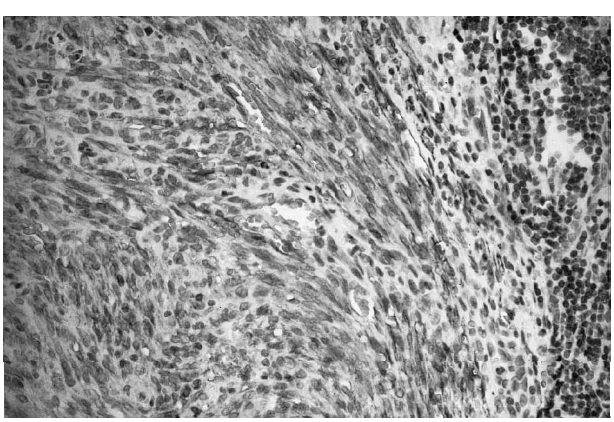

FIG. 3

High magnification of spindle cell proliferation of KS showing clear CD 34 antigen immunoreactivity (× 250).

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Sweden) and the ALFexpress DNA sequencer (Amersham Pharmacia Biotech, Uppsala, Sweden). The sequence obtained was identical to that previously described as the KS330 *Bam* HHV8 fragment.[15]

Discussion

KS is considered to be a virus-associated multifocal neoplasm. It commonly begins with multiple reddish-purple macules or papules in the skin that usually involve the lower extremities with a proximal spread, and many of the lesions evolve into plaques and finally into subcutaneous nodules.[3,16] Histopathologically, progressive clinical features usually correspond to the inflammatory, angiomatous, granulomatous and sarcomatous evolution. Although lymph node involvement may be seen in all four clinical forms and sometimes can precede the development of skin lesions or may even occur in their absence,[17] it is more frequently seen in the lymphadenopathic and AIDS-related forms.[16] On the basis of the clinical evaluation, a differential diagnosis of KS includes post-inflammatory hyperpigmentation, prurigo nodularis, blue naevi, malignant melanoma, and cutaneous lymphoma. Histologically, KS should be distinguished from dermatofibroma, haemangioma, fibrosarcoma, well-differentiated angiosarcoma, bacillary angiomatosis, acroangiodermatitis and pyogenic granuloma.

As is well known, KS occurs in many patients with AIDS and, undoubtedly, is one of the most common AIDS-associated malignancies in a large percentage of them (15–20 per cent). In AIDS patients, KS is more clinically aggressive and often characterized by visceral involvement, especially of the upper and lower gastrointestinal tract. In particular, parotid enlargement in the patients has often been described in children and adults, and is usually associated with general lymph node involvement. Although the parotid lesion in our patient could not be considered as a primary KS of the parotid (which has been described as an extremely rare condition), our lesion can be considered as an interesting example of KS with an extremely uncommon presentation. After the histopathologic diagnosis of KS, an accurate dermatological investigation was necessary to disclose the small cutaneous lesion on the left foot. It was also possible to demonstrate in the patient's lesions a direct molecular positivity for the HHV8 infection. It follows that the long stay of the patient in Africa as a teacher and the immunological and molecular positivity for HHV8 suggest a KS related to HHV8 infection contracted in a country in which KS is endemic. Furthermore, the increased risk of the development of a KS in a European population after a long stay in Africa has been postulated.[18] However, since the incidence of HHV-8 seroprevalence in the area of Italy from which the patient came, is considered high,[19] a sporadic KS cannot be excluded.

In 1983, Puterman and Goldstein[11] reported one case of intraparotid lymph node KS which represented the first example of primary KS of an intraparotid lymph node in a patient without immunological deficiency. In 1988, Josephson *et al.*[12] reported the second case of primary KS of an intraparotid lymph node in a non-immunocompromised patient. Another case of the pathology in a 65-year-old female was added in 1992 by Bonzanini *et al.*[13] Cutaneous lesions were not described in any of the lesions, and immunodeficiency or a direct correlation to HHV8 infection was not demonstrated. However, the follow-up was no longer than one year in any of the series.

Although the initial diagnosis of our case was 'primary KS of an intraparotid lymph node', after the accurate dermatological investigation and four years of follow-up, we could appreciate the indolent progression of the disease with the development of multiple small cutaneous lesions all over the body. Despite the occurrence of new cutaneous lesions, the general health of the patient was not compromised, and no other lymph node involvement was demonstrated.

Treatment strategy of KS should be tailored on the basis of the clinical forms and stage. Observation alone may be adequate for immunocompetent asymptomatic patients, but symptomatic resectable lesions can be approached by surgery. Advanced disease or unresectable lesions instead need radiation therapy.[20] In the primary localized form, or forms with limited numbers of cutaneous lesions, a few treatments of cryotherapy with liquid nitrogen have been demonstrated to be effective.[21] Intralesional therapy with vincristine or bleomycin has been proposed for the treatment of cutaneous and intraoral lesions,[22] whereas sclerotherapy with three per cent sodium tetradecyl sulfate has been proposed for intraoral nodular lesions.[23] KS can be managed by irradiation alone when the reduction of a huge intra-oral or lymph node mass is required.[20] In advanced stages of the disease, or if the other approaches fail, chemotherapy is appropriate. Commonly used agents include doxorubicin, daunorubicin, bleomycin, vincristine, and vinblastine. Zidovudine in association with chemotherapy is found to be effective in AIDS-related KS.[24] Patients with AIDS-related KS and with CD4 counts of less than 200 cells/mm^3 have a high mortality risk despite treatment.[25] The role of interferon in the treatment of KS is still unclear,[26] although it has also been proposed in the treatment of cutaneous lesion of sporadic KS as an intralesional agent.[27] In our case, interferon therapy was not delivered because it was considered contra-indicated by the patient's heart condition. The surgical removal of the mass with a subtotal parotidectomy was clearly adequate since after four years no recurrence in the parotid region was observed, but five cycles of chemotherapy with vincristine did not hinder the slow evolution of the cutaneous lesions.

In general, prognosis is variably related to many intercurrent factors such as immunological competence of the patient, the stage of the disease or concomitant infections.[3] In all cases of non-immunocompromised patients reported in the literature in which the parotid was found to be the only localization of KS, no parotid recurrence or cutaneous lesions were demonstrated after surgical removal. However, the maximum follow-up of one year may not be adequate for a disease with a such an 'indolent and waning course'.[3]

Conclusion

On the basis of the clinical history of our patient and the laboratory data, although a sporadic KS cannot be excluded, we can presume that there is a correlation between the stay of the patient in Africa and the HHV8 infection. As a consequence, the clinical form should be included as an endemic African form, which developed in a European in whom the rate of spread of the lesions generally tends to be slower. The four-year follow-up without parotid recurrence supports the adequacy of a local surgical procedure, as previously reported for primary KS of intraparotid lymph nodes.

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