Kaposiform hemangioendothelioma in an adult with rheumatoid arthritis

M. FILOTICO1, R. FILOTICO2

1 Department of Anatomic Pathology, Ospedale Fond. Card. Panico, Tricase (LE), Italy; 2 Dermatology Unit, Ospedale “Perrino”, Brindisi, Italy

Key words
Vascular tumors • Kaposiform hemangioendothelioma

Summary
This report describes a case of kaposiform hemangioendothelioma arising in an adult man during the course of rheumatoid arthritis treated with steroids and methotrexate. The vascular proliferation began in the terminal phase of the disease, which culminated in acute renal failure and death. We discuss the possible relationship between rheumatoid arthritis, its treatment, and the onset of vascular proliferation, as well as the role of kaposiform hemangioendothelioma in aggravating the autoimmune disease and leading to its fatal outcome.

Introduction
Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor of intermediate (borderline) malignancy that occurs mainly in infants and children. KHE is characterized by infiltrating nodules and sheets of spindle cells, affecting the skin and soft tissues of the extremities. Morphologically, it is highly similar to Kaposi’s sarcoma, although the biologic behavior of KHE is not fully characterized. KHE patients die as a result of extensive local disease or from a frequent complication called Kasabach-Merritt phenomenon (thrombocytopenia, microangiopathic hemolytic anemia, and consumptive coagulopathy).

KHE is even more rare in adults. The occurrence of this lesion in an adult, in association with an autoimmune disease treated with steroids and methotrexate and leading to a quick lethal outcome, makes this case worthy of interest.

Case presentation
A 48-year-old Italian man presented to the Dermatology Unit with skin rashes of purplish-brown color, mainly on the limbs, which he had had for about 6 months. He reported that, since the age of 30, he had recurrent episodes of joint pain accompanied by fever. He had been diagnosed with serum-negative rheumatoid arthritis (RA) and had been under treatment with steroids and methotrexate. The patient also reported that, at the age of 46 years, he had been hospitalized for glaucoma of the right eye. On that occasion, laboratory testing revealed neutrophilic leukocytosis (12,000/mm3) and high plasma fibrinogen (520 mg/dl), confirming the diagnosis of RA. Based on the features of the rash and the patient’s immunosuppressive therapy, we suspected Kaposi’s sarcoma. Therefore, a biopsy of skin and subcutaneous tissue (3x2x1 cm3) was taken from an affected area on the left leg; it was fixed in formalin and embedded in paraffin for routine and immunohistochemical analyses.

Hematoxylin-eosin staining revealed a brisk microvascular proliferation at the dermal and hypodermal levels (Fig. 1a). The vascular component consisted of well-formed capillaries whose endothelium was voluminous and prominent (Fig. 1c). The vascular lumen was engulfed by thrombotic material (Fig. 1c-d). The stromal elements were globoid and spindled, arranged disorderly (Fig. 1b). Mitotic activity was not seen.

There was a glomeruloid pattern of capillary proliferation (Fig. 2a-b). Gomori’s silver stain also revealed glomeruloid dermal and hypodermal nodules (Fig. 2c-d). These observations excluded Kaposi’s sarcoma. Immunohistochemical analysis showed strong positivity for CD34 (Fig. 3a-b) and CD31 (Fig. 3c) in the endothelial elements, while stromal cells were negative for these.
antigens. Pericytes were positive for smooth muscle actin (Fig. 3d). The sample was negative for human herpes virus 8 (HHV8), ruling out Kaposi’s sarcoma (Fig. 3e). The Ki-67 labeling index was < 1%, indicating a low level of proliferation. Altogether, these findings supported a diagnosis of KHE.

Three months later, the patient was hospitalized because of the collapse of several vertebral bodies due to osteoporosis. A few days later he developed acute renal failure with normal values of platelets (268,000 cells/mm3), RBCs (5,200,000 cells/mm3) and WBCs (8,500 cells/mm3). Prothrombin time was 74% and the partial thromboplastin time (33 s) was in the normal range. In contrast, there was high serum fibrinogen (535 mg/dl) and D-dimer (7,004 ng/ml), indicating an aggravation of RA, high serum myoglobin (3,532 ng/ml) indicating muscle damage, and hyperkalemia (7.3 mEq/l). The patient died within a few hours. Testing for HIV was not carried out nor was an autopsy performed.

Discussion

This report illustrates the case of a middle-aged man who developed KHE in the context of immunosuppressive treatment for RA. The diagnosis of KHE was established on the basis of the histologic and immunohistochemical findings that, together with the HHV8 negativity, excluded Kaposi’s sarcoma. The patient’s death
was attributed to a rapid aggravation of RA, with signs of muscle damage and electrolyte imbalance, in the absence of Kasabach-Merritt phenomenon. The first record in PubMed of KHE in adults dates back to 1997. From that date, 16 other reports have appeared in the literature. These are mostly reports of single cases or miniseries of no more than three cases, for a total of 20 cases as indicated in Table I. In the same period, two series of 33 and 107 cases concerning childhood KHE have also been published. The appearance of KHE at an early age in association with other malformative vascular lesions (e.g. lymphangiomatosis) suggests a congenital etiology. An onset of KHE in adulthood, instead, suggests a pathogenetic mechanism of an acquired type. Indeed, several cases of KHE developed in the context of other diseases, such as osteomyelitis treated with repeated surgeries, lupus erythematosus disseminatus with chronic renal failure, hepatitis C and trauma, hepatitis C with cirrhosis, and RA (this case). Based on these observations, we suspect that even other reported cases of adult KHE may have arisen in the context of another disease, that however, was not described.

The clinical presentation of KHE mimics very closely that of Kaposi’s sarcoma. In contrast, the histopathology of the lesions differs substantially from classic Kaposi’s sarcoma, in both architecture and cytology. The vascular proliferation in KHE always consists of well-formed capillaries with an evident peripheral argyrophilic reticulin and a pericytic component; it can be diffuse or produce nodular aggregates that are glomeruloid and that affect the dermis and hypodermis. The differential diagnosis is also supported by immunohistochemical analyses: in KHE expression of CD34 and CD31 is restricted to endothelial cells and does not affect stromal cells, whereas in Kaposi’s sarcoma the stromal cells are also positive. In KHE, staining for smooth muscle actin highlights pericytes that are absent from classic Kaposi’s sarcoma lesions. The constant negativity for HHV-8 in KHE is discriminating in the differential diagnosis.

Our patient did not develop Kasabach-Merritt phenomenon, which is a frequent complication of KHE in childhood that often leads to death. In the two case series of childhood KHE, the incidence of Kasabach-Merritt phenomenon was 56%. In the 20 cases of adult KHE, this deadly complication was reported only once, in a patient with hepatitis C cirrhosis. The HIV status of our patient was not tested. None of the 20 reported cases of KH in adulthood were associated with HIV, although a retrospective survey of 52 HIV-positive patients (ages not reported) in a Mexico City hospital found one association with KHE. In the opinion of the authors of

![Fig. 2. Glomeruloid pattern of capillary proliferation shown with hematoxylin and eosin (a, 100x) and Masson's trichrome stain (b, 100x). Glomeruloid dermal (c) and hypodermal nodules (d) (Gomori's silver stain, 40x).](image-url)
that report, the case of KHE had “no relation with HIV infection” 20.

Histologically, KHE presents evident similarities with juvenile hemangioma [6]. KHE is even more similar to tufted angioma (angioblastoma of Nakagawa), a benign vascular tumor that presents as a macule or nodule. Indeed, some have proposed that KHE is the disseminated form of tufted angioma and, therefore, a benign lesion itself 6 15.

In conclusion, on the basis of this case and the literature, it seems that the onset of KHE in adults, more than an autonomous phenomenon as happens in childhood, is an epiphenomenon accompanying another pathology. This etiology could explain the low incidence of Kasabach-Merritt phenomenon and the more severe course of the disease. That the appearance of KHE may be iatrogenic, in our case, seems unlikely since the same drugs administered to patients with RA (e.g. steroids, antineoplastic agents) are used also to control this disease 21. It is to be noted, also, that the beginning of the worsening of the underlying disease coincided with the onset of the manifestations of KHE. The present state of knowledge does not allow one to know if the appearance of KHE in the course of a morbid process is the cause or the consequence of its worsening.

References