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Case Report

Pleural Kaposi sarcoma: an unusual clinical case

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Summary
Kaposi sarcoma is a low-grade mesenchymal tumor associated with human herpesvirus-8. Here we describe the case of a 37-year old woman, who underwent to kidney and liver transplant for congenital hepatic fibrosis and bilateral polycystic kidney, with successive immunosuppressive therapy. After 5 years from first transplant, she developed cutaneous, mucosal, pleural and nodal localizations of Kaposi sarcoma, without lung lesions. Because of an initial clinical presentation with an important nodal and pleural involvement, a diagnosis of a lymphoproliferative disease was suspected. Pathological examination of the pleural sample allowed to exclude lymphoproliferative neoplasia and was consistent with Kaposi sarcoma. Subsequently involvement of other sites was diagnosed as expression of diffuse disease. The interest of this case lays in the unusual clinical presentation which can lead to diagnostic pitfalls when evaluating pleural biopsies.

Key words: Kaposi sarcoma, transplant, pleura

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Introduction

Kaposi sarcoma (KS) is a low-grade mesenchymal tumor, usually locally aggressive, involving blood and lymphatic vessels. Human herpesvirus-8 (HHV8) plays an important role in the pathogenesis of KS.
This neoplasm is a well-known sarcoma that can develop in immunodeficient patient, being the most common neoplasm in untreated patients with HIV.
There are different variants (Tab. I) of KS, among which we can observe KS related with immunodeficiency, i.e. the AIDS – associated KS and the iatrogenic KS. The first subtype is related to AIDS patient and it is usually the most aggressive variant. The second one is the iatrogenic form that is related to immunosuppressive treatment, typically arising months or years after solid-organ transplantation [1]. This subtype is relatively uncommon and its course is unpredictable.
In iatrogenically immunosuppressed patients, there is an increased risk for development of KS: KS is reported to comprise 5.7% of all de novo malignancies in recipients of solid organ transplantations at an average of 22 months after transplantation.
The incidence of KS in solid organ transplant recipients is about 60 times higher than at general population, with risk increasing over time, especially after 5 years.
The risk is higher in patients who have undergone transplantation of multiple organs, followed by recipients of liver and renal transplantation [2].
The skin is one of the first affected sites, but mucosal membranes, lymph nodes and visceral organs can be involved. The most frequent visceral lo-

Table I. WHO Classification of Tumors (Soft Tissue and Bone Tumors, 5th Edition) divides KS in four subtypes with several clinical features and different outcomes.

Subtype	Classic KS	Endemic African KS	AIDS-associated KS	Iatrogenic KS
Epidemiology	Elderly men, Mediterranean, eastern European, Ashkenazi Jewish	Middle-aged adults and children, African	Untreated AIDS	Solid-organ transplant recipients treated with immunosuppressive therapy
Typical localization	Skin (distal extremities)	Skin, lymphadenopathic form in children)	Skin, mucosae, lymph node, visceral (mainly gastrointestinal tract)	Skin, lymph node, visceral
HHV-8	+	+	+	+
HIV	-	-	+	-
Prognosis	Indolent	Protracted course, letal in lyphadenopathic form in children	Aggressive	Unpredictable course, usually it may resolve upon immunosuppressant withdrawal

calizations in transplanted patients are the gastrointestinal tract and lung [3]. Lung is the characteristic intrathoracic localization of KS and only few papers report cases of lung involvement, with secondary pleural infiltration [4-5]. In these cases, the reported pleural KS were of the AIDS-related subtype and, to our knowledge, there are no cases reported in transplanted patients [4-5].

Histologically, KS is characterized by a poorly circumscribed infiltrative overgrowth of cleft-like spaces, lined by fusiform endothelial cells, associated with extravasated erythrocytes and inflammatory lymphocytic infiltrate, in different proportion depending on the stage of the lesion. The presence of intracellular or extracellular hyaline globules is frequent.

The main differential diagnosis may be with reactive fibrous tissue especially in early stages without malignant features, lymphangioma or hemangioma in cases with rich pseudo-vascular proliferation and angiosarcoma in cases with sever atypia tissue.

Immunohistochemistry is an important tool when suspecting KS, since HHV-expression with nuclear pattern is mandatory for the diagnosis and helps in the differential diagnosis with angiosarcoma or reactive lesions.

Case report

We describe the case of a 37-year old woman with a history of previous kidney and liver transplant.

Her medical history began at the age of 4 years. Congenital hepatic fibrosis was diagnosed in association with bilateral polycystic kidney leading to the diagnosis of Autosomal Dominant Polycystic Kidney Disease (ADPKD) associated with portal hypertension, splenomegaly, numerous duodenal angiectases and secondary leukopenia and thrombocytopenia.

Throughout her life she experienced multiple episodes of sepsis of biliary and urinary origin, asthmatic bronchitis with frequent exacerbations and persistent anemia and thrombocytopenia that required frequent blood transfusions since the paediatric age.

She underwent kidney transplant at the age of 32 years from a living donor with good improvement of renal function, and liver transplant at the age of 36, followed soon after by a re-transplantation because of thrombosis of the hepatic artery.

Immunosuppressant therapy was achieved with tacrolimus and steroids.

Four months after the liver transplant, the patient presented to the emergency room with sudden onset right hematic pleural effusion of unknown origin and low blood platelet count, down to 22,000/mcL. Pleural drainage was performed with evacuation of 500 cc of hematic liquid and a thorax-abdomen CT scan was obtained, with evidence of right pleural effusion and pleural thickening on the diaphragmatic side, associated with multiple deep seated lymphadenopathies, above and below the diaphragm, up to 3 cm in greatest dimension (Fig. 1A).

The subsequent FDG-PET scan demonstrated pathological uptake by the CT described lymphadenopathies and the pleural thickening.

Cytological examination of the drained pleural effusion demonstrated only red blood cells.

Because of the diffuse lymphadenopathies, a clinical and radiological diagnosis of “suspected lymphoproliferative neoplasm” was made and the patient underwent Video-Assisted Thoracic Surgery (VATS) pleural biopsy, with a request of frozen section evaluation to judge adequacy of the samples for a definitive diagnosis.

On frozen sections, a rich acute inflammatory infiltrate, with a moderate amount of activated fibroblasts and reactive sclerosis were disclosed. No localization of lymphoproliferative disease was noted. (Fig. 1B).

Permanent histological sections of the pleural biopsies displayed replacement of whole fragments by

spindle shaped cells proliferations with formation of slit-like vascular lumina (Fig. 1C). At higher magnification, nuclear hypercromasia, some atypical mitosis, intracytoplasmic eosinophilic inclusions and intracy-

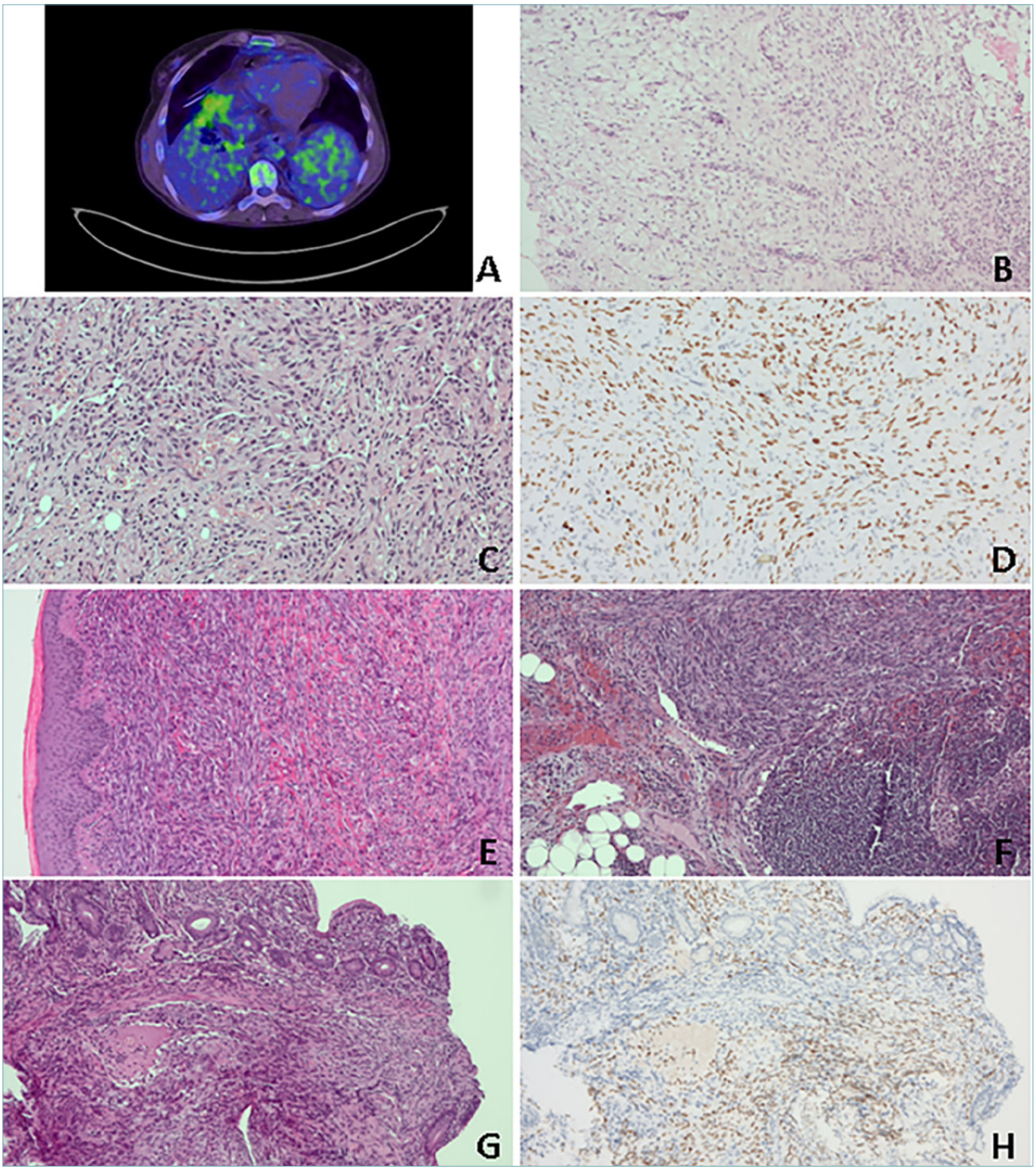

Figure 1. TC image with pleural effusion, without lung lesions (A). Frozen section of pleurisy, performed during VATS, without evidence of lymphoproliferative disease (hematoxilin-eosin, 100X) (B). In FFPE histological sections of the pleural biopsies, some fragments were occupied by a spindle shaped cells proliferations with formations of slit-like vascular lumina (hematoxilin-eosin 100X) (C). The neoplastic proliferation was HHV-8 immunoreactive (100X) (D).

toplasmic lumina containing erythrocytes were evident. These cells were reactive for antibodies against CD31, CD34, ERG-1 and HHV-8 antigens (Fig. 1D). A final diagnosis of "pleural localizations of Kaposi sarcoma" was performed.
Serological assessment excluded infection by HIV, but showed high level of HHV-8 serum antibodies.
To exclude a concomitant lymphoproliferative disorder and to determine the nature of the CT described lymphadenopathies, an excisional lymph node biopsy was performed.
At the same time, some cutaneous lesions recently arising on the back were excised for histological evaluation.
At histological examination, skin lesions and lymph node shared the same features with the pleural lesion, consisting in a proliferation of spindle cells, immunoreactive for HHV-8 pointing to KS.
Staging was completed with gastrointestinal endoscopy revealing the presence of duodenal hyperemic areas which were biopsied and received a diagnosis of KS involvement.
Thus we concluded for disseminated Kaposi sarcoma with cutaneous, lymph nodes, pleural and duodenal involvement, in a transplanted non-HIV patient.
The patient was alive at follow-up, 17 months later.

Discussion and conclusions

This case is characterized by an unusual clinical presentation and at our knowledge, there are no papers reporting a pleural KS, without lung involvement. A few reports describe pulmonary and pleural KS in cases of AIDS-patients [4-5]. In our case, the patient was HIV negative and had received immunosuppressive therapy for kidney and liver transplantations.
Typical involved sites in KS are skin, mucosal membranes and lymph nodes; other visceral localizations are less frequent, among which the lung. Pleural KS is rare and usually extending from lung lesions [4-5].
On the contrary, in our case KS is limited to the pleura without a lung involvement and to lymph nodes above and below the diaphragm as supported by lung PET and CT scan.
Accurate staging with histological demonstration of KS involvement in the lymph node, skin and duodenal sites were conclusive to exclude a coexistent lymphoproliferative disease, which is not infrequent in immunodeficient patients [5].
This case shows us that, in the setting of a iatrogenic immunosuppressed patient presenting with hematic thoracic spilling, KS involvement of the pleura has to be taken in consideration, although in the absence of visceral involvement and/or early cutaneous presentation. Intraoperative examination can be very challenging and in our case, we were asked to evaluate the adequacy of a pleural sample during surgery with the suspect of lymphoma and, on frozen sections, we concluded acute pleurisy. On permanent sections, a nodule became evident with the morphological aspect of KS subsequently confirmed by immunohistochemical positivity for HHV-8.
As in our case, the cytological inadequacy of a hematic specimen and the histological features of acute pleurisy can hide a KS; in fact, alterations of the activated fibroblasts and the acute inflammation can mask the lesion. Spindle cells can be interpreted like reactive modifications, also because the nuclear atypia in KS cannot be particularly pronounced.
Furthermore, enlargement of lymph nodes contributes to feed the differential diagnosis with lymphoproliferative disorders, particularly in a clinical setting of immunosuppression.
An appropriate immunohistochemical panel including HHV-8 should be used evaluating tissues as pleura, not a common site of KS, characterized by spindle cell pseudovascular proliferation to exclude or to confirm a KS.

Conflict of interest

The authors declare no conflicts of interest.

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Ethical consideration

None.

Author contributions

All listed authors contributed to the production of this manuscript and are listed in the appropriate order.

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