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Variable clinical presentations of Classic Kaposi Sarcoma in Turkish patients

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Abstract

Background: Kaposi sarcoma (KS) is a vascular neoplasm with multicentric cutaneous and extracutaneous involvements, which was first described by Moriz Kaposi in 1872. Since then, different epidemiological clinical and histopathological variants of this neoplasm have been identified. Classic Kaposi sarcoma (CKS) is one of four main clinico-epidemiologiologic variants. characteristics of the disease.

Materials and Methods: Four Turkish inpatients with CKS were evaluated in the study. All medical history and clinical data were noted. A screening immunodeficiency workup were performed for all patients. HHV-8 immunofluorescence testing on the specimens and ELISA test for human immunodeficiency virus (HIV 1 and 2) were performed. Pulmonary X ray graphies and computurized tomography (CT) scan were applied. Stage of the tumor was determined, in each case, according to the classification system proposed by Brambilla *et al* in 2003.

Results: All patients are positive for HHV-8. They were all immunocompetent and negative for HIV1 and HIV2. The first patient was unusual for morphological presentation of several verrucoid lesions that was evaluated as verrucoid KS. He was considered stage IB CKS. The patient 2 was a young man and the course of KS seemed unexpectedly aggressive for CKS. His clinical appearence seemed us to be a patient with AIDS-associated KS. The patient was evaluated as stage IVB CKS. Our third patient had also prominent lymphedema associated with bluish discoloration on the toes and fingers, suggesting a diagnosis of peripheral vascular disorder. He was diagnosed as stage IIIB CKS. The fourth case was interesting for very extensive lesions involving big sized plaques and also the existence of mucosal lesion. The patient was diagnosed as stage IVB CKS.

Conclusions: It seems that the reports of exceptional cases of KS are accumulating. Data from various cases should be collected and perhaps, novel clinical classifications should be considered. (*J Dermatol Case Rep*. 2012; 6(1): 8-13)

Introduction

Kaposi sarcoma (KS) is a vascular neoplasm originating from vascular and lymphatic endothelia. It was first described by Moriz Kaposi as the idiopathic multiple pigmented sarcoma of the skin in 1872.[1,2] Human herpesvirus 8 (HHV-8) is considered to play an important role in etiology, because DNA sequences of the virus have been recently detected in almost all KS lesions.[1-4] Although, important advances have been recently made, the cause is still unclear as in all cancers and KS continues to remain enigmatic.

There are basically four clinical-epidemiological types of the disease. The original classic type, African or endemic type, iatrogenic or immunosuppressant related type and epidemic or AIDS related type. Classic KS (CKS) is primarily a skin disease of the lower extremities affecting predominantly elderly men of Mediterranean origin; predominantly Jews, Italians and Greeks.[1-4] This type has a relatively indolent course and a typical clinical presentation with a combination of red-purple macule, papule, nodule and/or plaques on the lower extremities and/or hands. Mucosal involvement, particularly oral and/or oropharyngeal mucosae, is uncommon in this type. Nevertheless, other three types tend to involve the skin, visceral organs and mucosae more extensively and to run more aggressively. Histopathological features depend on the stage of the disease in CKS. Furthermore, another

histologic variants have also been reported in recent years.[4,5]

CKS is relatively common in Turkey.[6,7] We present four cases with unusual clinical presentations for CKS in HIV negative patients. All patients were immunocompetent and did not have another disease.

Materials and Methods

Four Turkish inpatients with KS were evaluated in the study. All medical history and clinical data were noted. The patients had no family history for similar lesions or KS. CKS was proven by cutaneous biopsies and immunohistochemical stains. A screening immunodeficiency workup were performed for all patients. Quantitative natural killer cell count, B and T cell lymphocyte counts and immunoglobulin analysis were within normal limits. HHV-8 immunofluorescence testing on the specimens and ELISA test for human immunodeficiency virus (HIV 1 and 2) were performed. Pulmonary X ray graphies and computurized tomography (CT) scan were applied. Positron emission tomography (PET)/CT scan and endoscopic examination were used as further screening methods, if necessary. Stage of the tumor was determined in each case according to the classification system proposed by Brambilla *et al* in 2003[8] (Table 1).

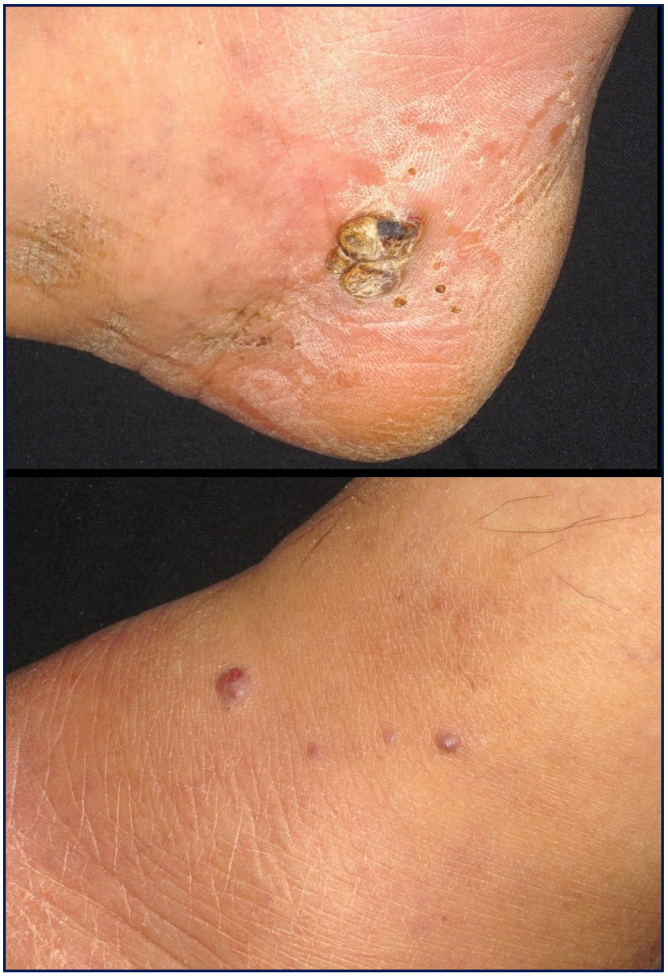

Figure 1

Purplish papulonodular lesions around the right ankle.

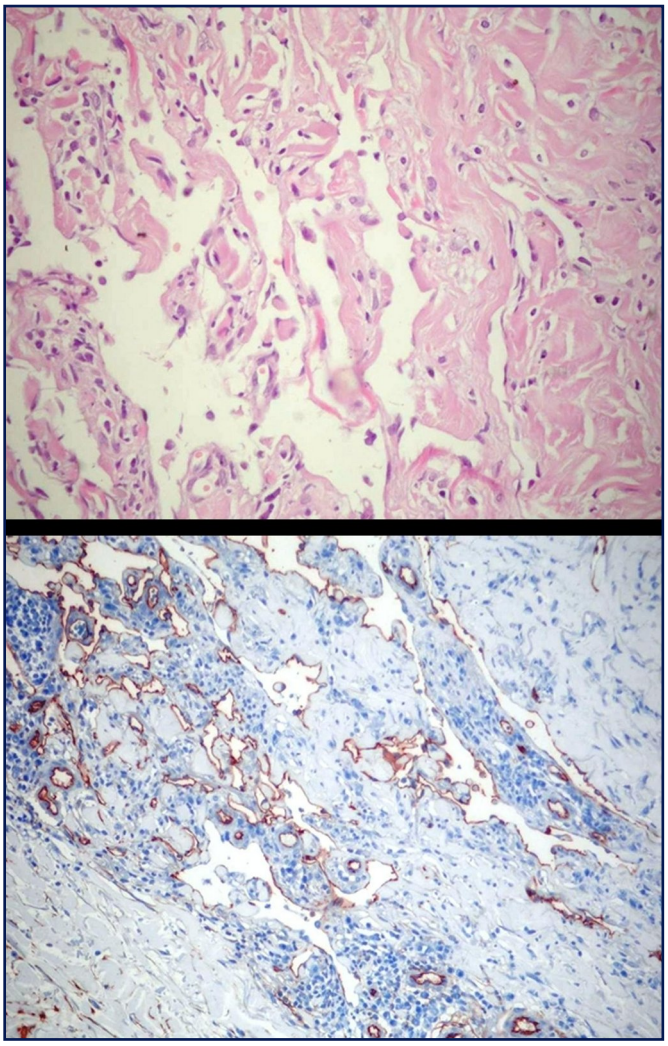

Figure 2

Presence of vascular slits and spindle cells and CD 34 staining in many vessels.

Results

CASE 1

A 74-year-old man was admitted to our clinic with an unhealing wound on the medial side of the left foot. Dermatological examination showed a nodular lesion sized 1.5 x 2 cm covered with a yellowish hyperkeratotic crust similar to cutaneous horn and several purplish papulonodular lesions around the right ankle (Fig. 1). Lymphadenopathy was not present. Laboratory investigations revealed normal results except for hyperglycemia, hyperlipidemia and a high blood creatinine level. Pulmonary X Ray, CT of thorax and abdominal were normal. Biopsies and immunohistochemical stains from one nodule and hyperkeratotic lesion were assessed as KS with the presence of vascular slits and spindle cells and CD 34 staining in many vessels (Fig. 2). HHV-8 was detected in the lesional skin sample. The patient was considered stage IB CKS. Cryotherapy for papulonodular lesions and local excision for hyperkeratotic lesion were performed and follow up was planned.

CASE 2

A 27-year-old man referred to our clinic with reddish-purplish swellings on his ears, nose and chin. These lesions have been existed for one year. He initially had inguinal swellings 8 years ago and the diagnosis of KS had been already made at another medical center. He had received 2 sessions of chemotherapies and had been told to have remission. The patient denied smoking, alcohol, intravenous drug use and homosexual activity.

Dermatological examination revealed several purple-red nodules on the right helix, mental region, the right retroauricular region and at the tip of the nose (Fig. 3). Mucosal involvement did not exist. Multiple mobile lymphadenopaties were present in the axillary, cervical and inguinal regions. Hemogram and biochemical tests were within normal limits and serologic tests for HIV were negative. Pulmonary X-Ray was normal. Multiple lymphadenopathies were detected in thoracal and abdominal CTs. Biopsy from one of the cutaneous nodules confirmed KS with the proliferation of monotonous spindle cells including mitotic figures and vascular splits in various sizes. Immunohistochemistry for HHV-8 showed nuclear pattern of staining. The patient was evaluated as stage IVB CKS. Chemotherapy and radiotherapy were planned for the treatment.

CASE 3

A 73-year-old man has had edema on his lower extremities and purplish skin color on the toes bilaterally for two years. He had applied to vascular surgeons for several times and had been followed up as a patient of venous insufficiency. Dermatological examination revealed moderate, non-pitting bilateral edema on both of the lower extremities and indistinct reddish-purplish skin discoloration on the dorsum of the feet and toes. Similar lesions were also present on the third and fourth fingers of the left hand. Lymphadenopathy was not detected. All laboratory investigations including blood chemistry, hemogram, HIV serology, pulmonary X-Ray, thorax CT revealed normal results, but abdominal CT showed a 2x4 cm gastric mass which was evaluated as an anthral polyp by gastroscopy and biopsy results. Mild gastritis and mild intestinal metaplasia were detected. Histopathological analysis of bluish macules on the leg was consistent with lymphangioma like KS in which irregularly shaped and dilated vascular spaces between collagen fibrilles in reticular dermis was noteworthy. Immunoperoxidase staining for CD34 was positive (Fig. 4). Immunohistochemistry of HHV-8 showed positive staining in the tissue sample. He was diagnosed as stage IIIB CKS and was treated by local radiotherapy.

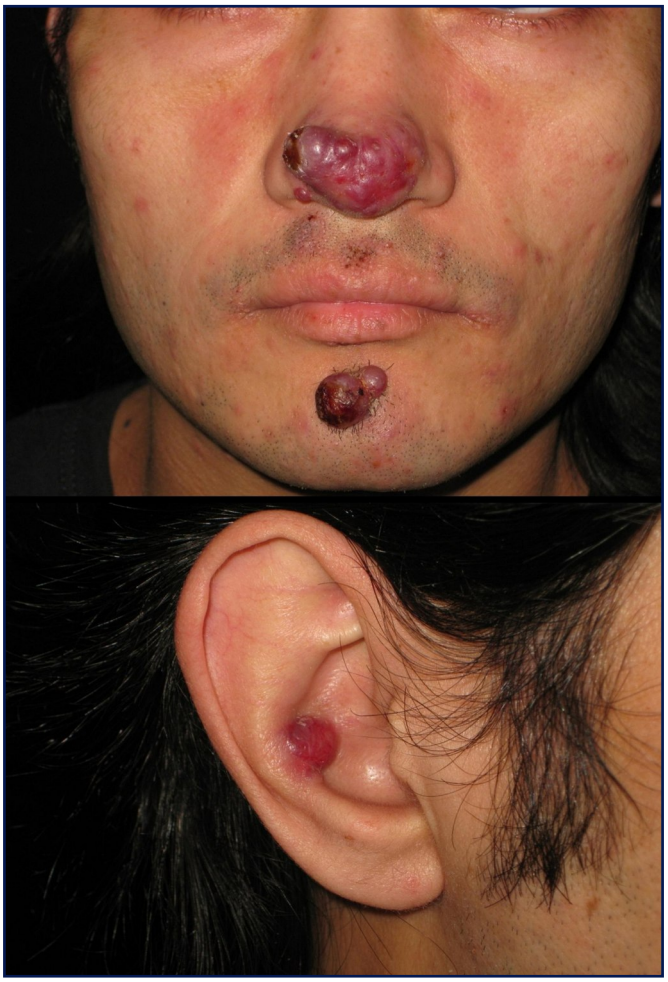

Figure 3

Purple-red nodules on the right helix, mental region and at the tip of the nose.

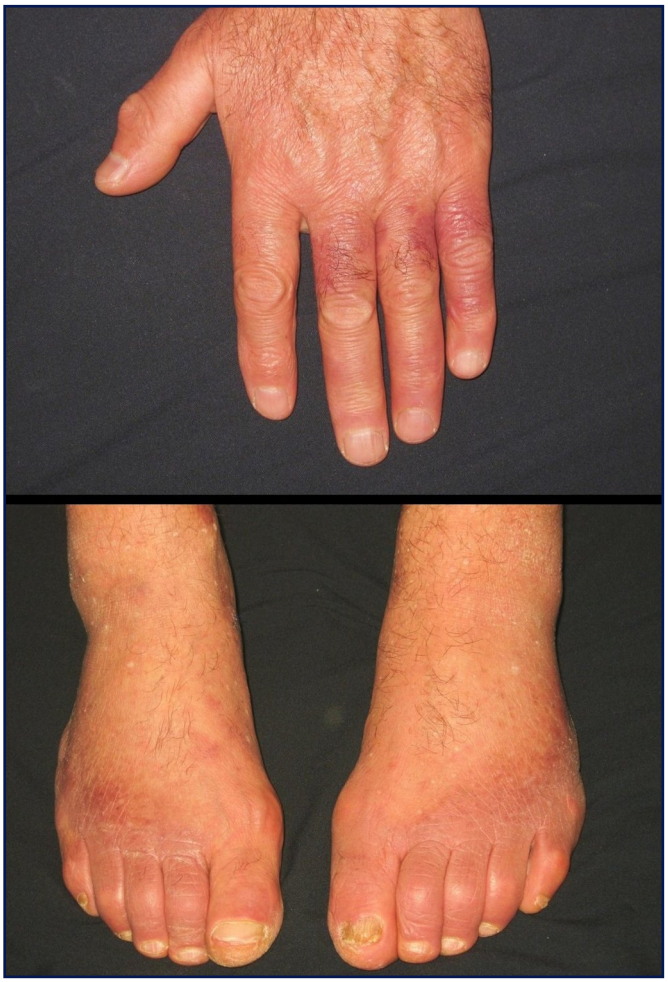

Figure 4

Reddish-purplish discoloration on the dorsum of the feet and the fingers of the left hand.

CASE 4

A 80-year-old man had reddish-purplish plaques on all his body, which involved extremities more than the trunk. The lesions have been existed for 5 years. He was referred to our clinic with a prediagnosis of cutaneous vasculitis. Diabetes mellitus and appendectomy were present in his personal history. He had quitted alcohol and cigarette smoking 25 years ago. Physical examination showed no abnormalities. Lymphadenopathy was not detected. Dermatological examination revealed purplish plaques in various sizes ranging from 1 cm to 10 cm on the extremities and also on the trunk (Fig. 5). One purplish-reddish plaque, ranging 2 x 3 cm, was present on his hard palatum as well. Routine laboratory investigations were unremarkable except for mildly high fasting blood glucose. Two biopsises, one from a purplish nodule on his foot and another from a purplish plaque lesion on his arm, revealed characteristic features of KS. In immunohistochemical examination, CD 34 staining was observed in a very large number of vessels infiltrating collagen fibrilles. HHV-8 was found in the lesional skin. Serological tests for HIV were negative. Abdominal and thoracic CT scans were performed in which hypodense nodular lesions with millimetric sizes in both lung segments and hypodense one nodular lesion in size of 2,5 x 1 cm in left adrenal gland were detected. Heterogeneity in thyroid gland and multiple lymph nodes, maximum of 1 cm in size, located in the aortacaval line were observed. PET/CT scan, gastroscopy, bronchoscopy and laryngoscopy were planned. While there was no involvement of the larynx in laryngoscopic examination, only erosive gastritis was detected in gastroscopic examination. There was no finding in favor of malignancy in PET/CT scan. The patient was diagnosed as stage IVB CKS, and electron beam therapy and chemotherapy were planned.

Discussion

KS appears to have some diversities of sociodemographical, clinical, and histopathological characteristics due to a different biological behaviour.[2,3,8] When epidemiological features are considered, some races and certain age groups such as middle aged and elderly Meditarrenean or Jewish men and male gender are prone to have more KS. However, KS patients with AIDS and African cases tend to be younger and the ratio of male/ female is also reversed. Clinical presentation may be highly variable as well.[1,2,3,9-12] Although typical lesions are livid macules, papules and nodules, almost 13 morphological variants have been described to date,

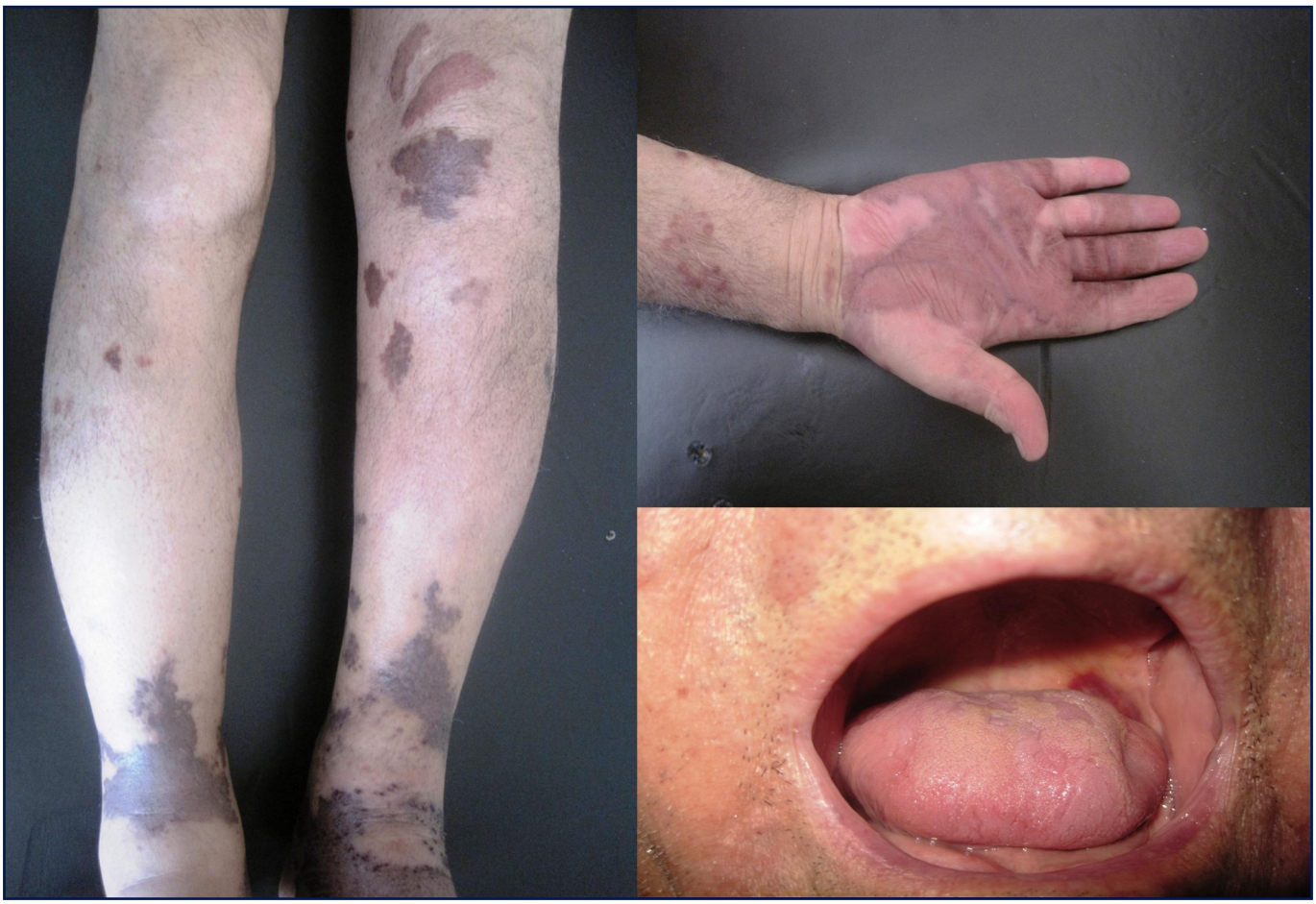

Figure 5
Purplish plaques on the extremities and the trunk.

which are patch, plaque, nodular, exophytic, infiltrative, keloidal, telangiectatic, cavernous, ulcerative, bullous and verrucous types.[1,13,14] These lesions may be localized without visceral involvement or aggressive with extensive visceral disease. Involvement of the oral and gastrointestinal tract, lymph nodes and the lungs may also occur. The course is aggressive particularly in patients with African and AIDS-KS and outcome of the disease is more fatal than that of patients with non AIDS-KS.[2,4,8]

All these epidemiological and clinical discrepancies of KS resulted in a need of producing a classification. Today, four main variants have been admitted on the basis of epidemiological and clinical criteria: Classic (elderly men of Mediterranean and Jewish extraction), endemic (Sub-Saharan Africans), iatrogenic (solid organ transplant patients and rarely other immunsuppressive patients), epidemic (HIV, AIDS, primarily homosexual men). The main characteristics of CKS are considered to be the onset at older ages, the preferential localization of the lesions on the lower extremities, the rarity of the involvement of the oral and gastrointestinal mucosae or internal organs and the slow progression extending to decades. Other subtypes of KS primarily occur in immunosupressive patients. African endemic type and AIDS-KS are characterized by aggressive disease with rapid course, rapid/multifocal dissemination and extensive internal organ involvement. Additionally, CKS itself exhibits a clinical and evolutional heterogenity that this situation is evident with some unusual case reports of CKS in the literature.[1,9-14]

As for our patients, the first patient was unusual for morphological presentation of several verrucoid lesions. Although hyperkeratotic-verrucous types were previously mentioned, the lesion was atypical with its horn-like appearance which made us think KS coexistent with squamous cell carcinoma (SCC) or de novo SCC, initially.[13] Nevertheless, the characteristic features of KS histopathology was shown in the biopsy specimens and it was evaluated as verrucoid KS.

The patient 2 was a young man and the course of KS seemed unexpectedly aggressive for CKS. His clinical appearence seemed us to be a patient with AIDS-associated KS. This patient had angiomatous nodules primarily on the acral regions of his head, on the tip of the nose, ears and retroauricular region. No other lesions existed anywhere. Serological tests for HIV declared negative results. The aggresive nature of the disease and distribution of the lesions were highly interesting despite the absence of AIDS or any condition with demonstrative immunosuppression. Aggressive CKS in immunocompetent patients has been very rarely reported in the literature.[15,16] In addition, while the involvement of the head and neck is 40-67% in HIV infected patients, it has been reported in only 14% of cases with CKS.[17] Sikora *et al.* suggested that even though most cases of KS are associated with immunodeficiency, clinical and laboratory proofs of this may remain inadequate; thus susceptibility to KS may be based on another unknown factor or inherited defect in host defence.[17]

Our third patient had also prominent lymphedema associated with bluish discoloration on the toes and fingers, suggesting a diagnosis of peripheral vascular disorder. Histopathological analysis revealing irregular ectatic vascular channels in reticular dermis and some papillary protrusion with inflammatory cells into wide vessel lumens provided to make the diagnosis of lymphangiomatous KS. When considered for histopathological presentations of KS, they are as numerous as clinico-morphological variants.[5] Hyperkeratotic, keloidal, micronodular, pyogenic granuloma-like, ecchymotic, anaplastic and lymphangioma-like KS have been described. Lymphangiomatous variant, which is seen in our third patient's skin specimens, is actually a rare variant occurring in less than 5% of KS cases.[5,18,19] The terms of "lymphangioma like KS" or "lymphangiomatous KS" may be used interchangeably. This histopathological type may be more related to some clinical variants such as bullous, lymphoedematous

Table 1. Mediterranean Kaposi's sarcoma staging.

Stage	Skin lesions	Localization	Behaviour	Evolution	Complications*
I - Maculo-nodular (± v)	Nodules and/or macules	Lower limbs	Non aggressive	Slow (A) Rapid (B)	Lymphedema Lymphorrea
II - Infiltrative (± v)	Plaques	Lower limbs	Locally aggressive	Slow (A) Rapid (B)	Hemorrhage Pain
III - Florid (± v)	Angiomatous nodules and plaques	Limbs, lower prevalent	Locally aggressive	Slow (A) Rapid (B)	Functional impairment
IV - Disseminated (± v)	Angiomatous nodules and plaques	Limbs, trunk, head	Disseminated aggressive	Rapid (B)	Ulceration

v: visceral involvement (pharyngo-oral cavity, gastroenteric tract, lymph nodes, bone marrow, lungs).

Rapid: increase in total number of nodules/plaques or in total area of plaques in the three months following an examination.

** All of them prevalent in stage III and IV, lymphedema and lymphorrea often observed in stage II, lymphedema and hemorrhage sometimes present in stage I.*

or hyperkeratotic KS.[14,15] Although, it was reported that bullae might be clinical hallmark of this type's histopathology, there are also another reports in which lymphoedematous type of KS histopathology had accompanied to marked lymphoedema clinically.[14,15,18-22]

The fourth case was interesting for very extensive lesions involving big sized plaques and also the existence of mucosal lesion. Clinical extensiveness and mucosal involvement may be unusual for a 5 years period of CKS in which a slow progression is anticipated. However, PET/CT scans showed no finding in favor of metastasis.

Conclusions

It seems that the reports of exceptional cases of KS are accumulating. Although genetic-individual and environmental factors may be responsible for it, pathogenetic basis of clinico-prognostic heterogenity of this unique disease produced by peculiar cases still remains to be investigated in detail. Data from various cases should be collected and perhaps, novel clinical classifications should be considered.

Acknowledgments

In our study, stage of the tumor was determined in each case according to the classification system proposed by Brambilla *et al* in 2003 (Brambilla L, Boneschi V, Taglioni M, Ferrucci S. Staging of classic Kaposi sarcoma: a useful tool for therapeutic choices. *Eur J Dermatol*. 2003; 13: 83-86. PMID: 12609790).

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