

# Pseudo-Kaposi Sarcoma: Differential Diagnosis from Kaposi Sarcoma

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**Background:** Pseudo-Kaposi sarcoma mimicks Kaposi sarcoma, both clinically and histopathologically. These conditions are due to congenital (Stewart-Bluefarb syndrome) or acquired (Mali) vascular malformations.

**Objectives:** The purposes of this study were aimed at evaluating the clinical and histopathological characteristics of pseudo-Kaposi sarcoma and finding differential diagnostic tools from Kaposi sarcoma.

**Methods:** Clinical information of 7 patients with pseudo-Kaposi sarcoma diagnosed in Asan Medical Center from 1989 to 1999 was obtained from the medical records and clinical follow-ups. We re-evaluated 10 biopsy specimens obtained from them and immunohistochemical studies for cutaneous lymphocyte antigen (CLA), CD34, vimentin, and factor VIII were performed with the standard streptavidin-biotin method using paraffin-embedded tissue specimens of 7 pseudo-Kaposi sarcomas and 3 Kaposi sarcomas. In addition, we examined whether human herpesvirus 8 (HHV8) was detected in 3 patients by polymerase chain reaction (PCR).

**Results:** Six male and one female patients were included. Mean age was 36.3 years. Three patients were classified into Mali type and the other four patients were into Stewart-Bludfarb type. Histopathological examinations revealed capillary proliferation in the upper dermis, perivascular infiltrate of inflammatory cells, extravasated red blood cells, and fibrosis of dermis. Anti-factor VIII and CD34 stained endothelial cells only. CLA was expressed in lymphocytic infiltrate in the epidermis and dermis of pseudo-Kaposi sarcoma, whereas it was negative in Kaposi sarcoma. PCR for HHV 8 showed negative results.

**Conclusions:** Pseudo-Kaposi sarcoma is an uncommon entity with characteristic clinical and histopathological features. Differential diagnosis between Pseudo-Kaopsi sarcoma and Kaposi sarcoma is important. We suggest that detection of HHV 8 by PCR and imunohistochemical study for CLA may be effective tools in the differential diagnosis between them.

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Pseudo-Kaposi sarcoma (PKS) is a vasoproliferative disorder that may resemble some cases of Kaposi sarcoma (KS) both clinically and histologically. Since Kopf and Gonzale<sup>1</sup> first described this condition as congenital dysplastic angiopathy in 1964, a variety of terms have been applied to similar cases of this condition, such as acroangiadermatitis<sup>2</sup>, arteriovenous (AV) malformations with angiodermatitis<sup>3</sup>, Kaposi-like AV malformation, and angioder-

matitis<sup>4</sup>. The term, "pseudo-Kaposi sarcoma" was first used by Earhart et al<sup>5</sup> in 1974 to describe a 24-year-old man with an AV malformation and skin lesions of angiodermatitis on the feet mimicking KS. The term 'Mali syndrome' has been applied to acroangiodermatitis secondary to chronic venous insufficiency, whereas it is called 'Stewart-Bluefarb syndrome' when it develops in patients with AV fistulae involving the limbs<sup>6</sup>.

We studied clinical and histopathological characteristics of PKS to find effective diagnostic tools for differential diagnosis from KS.

## MATERIALS AND METHODS

Clinical informations of 7 patients with PKS diagnosed in Asan Medical Center from 1989 to 1999 were obtained from the medical records and clinical follow-ups. To evaluate the clinical and histopathological characteristics of PKS, we re-evaluated 10 biopsy specimens obtained from them. To find effective tools for differential diagnosis between PKS and KS, immunohistochemical studies for cutaneous lymphocyte antigen (CLA; Becton-Dickinson, Lincoln Park, NJ, USA), CD34 (Immunotech, Marseille, France), vimentin (Zymed, South San Francisco, CA, USA), and factor VIII (Dako, Kyoto, Japan) were performed with the standard streptavidin-biotin method using paraffin-embedded tissue specimens of 7 PKS and 3 KS. We examined whether human herpesvirus 8 (HHV8) was detected in 3 patients with PKS and 8 patients with KS by polymerase chain reaction (PCR). DNA was extracted from the formalin-fixed, paraffin-embedded tissues. A 2- $\mu$ l volume of the DNA samples was used as a template for the

PCR. 5'-TCCGTGTTGTCTACGTCCAG-3' and 5'-AGCCGAAAGGATTCCACCAT-3' were used as the primers for amplification of the KS.

## RESULTS

### Patients Characteristics

Six male and one female patients were included. Mean age was 36.3 years. We classified these patients as Mali type or Stewart-Bluefarb type according to the previous report<sup>6</sup>. 'Mali type' has been applied to acroangiodermatitis secondary to chronic venous insufficiency. If PKS develops in patients with congenital hemangioma, AV malformations, or AV fistulae involving the limbs, we classified it into 'Stewart-Bluefarb type'. Three patients were classified into Mali type and the other four patients were into Stewart-Bluefarb type (Table 1). Mean age of Mali type (45.7 years) was older than that of Stewart-Bluefarb type (29.3 years). In patients with Mali type, the lesions developed in middle to old age (mean age of onset, 37 years), but PKS developed in early childhood in patients with Stewart-Bluefarb type (mean, 5 years). There were several associated diseases in these patients, of which varicose vein, Klippel-Trenaunay syndrome, and hemangioma may be related to the development of PKS. In a 6-year-old male child, PKS developed in the area adjacent congenital hemangioma on the sole.

### Clinical manifestations

PKS showed a variety of clinical manifestations comprised of irregularly reticulated patches to ulcerative lesions (Fig. 1). Patient 1 with Stewart-Bluefarb type showed AV malformation. Angiography revealed multiple abnormal vessels and mi-

Table 1. Clinical data of pseudo-Kaposi's sarcoma

| Patients                     | Sex/Age | Duration (year) | Associated diseases                    |
|------------------------------|---------|-----------------|--|
| <u>Mali type</u>             |         |                 |  |
| 1                            | M/34    | 2/12            | Wilson's disease                       |
| 2                            | M/45    | 25              | Varicose vein                          |
| 3                            | M/58    | 1               | Kidney transplantation                 |
| <u>Stewart-Bluefarb type</u> |         |                 |  |
| 1                            | M/40    | 35              | Protein S deficiency, A-V malformation |
| 2                            | F/48    | 37              | A-V fistulae                           |
| 3                            | M/23    | 20              | Klippel-Trenaunay syndrome             |
| 4                            | M/6     | 5               | Hemangioma                             |

**Fig. 1.** PKS showed varied clinical manifestations comprised of irregularly reticulated patches (A, B), and ulcerative lesion (C).

**Fig. 2.** Angiography revealed multiple abnormal vessels and micro-arteriovenous fistulae in patient 2 with Stewart-Bluefarb syndrome.

croAV fistulae in patient 2 with Stewart-Bluefarb syndrome (Fig. 2). There were no significantly different clinical findings between Mali-type and Stewart-Bluefarb type.

#### **Histopathological characteristics**

Histopathological examinations revealed capillary proliferation in the upper dermis, perivascular infiltrate of inflammatory cells, extravasated red blood cells, and fibrosis of dermis (Table 2). Al-

though there were several differences between Mali type and Stewart-Bluefarb type such as blood proliferation, fibrosis, and hemosiderin pigment, which were prominent in Stewart-Bluefarb type, as a whole, similar histopathologic findings were revealed. Acanthotic epidermis, mild infiltrate of inflammatory cells in the upper dermis, and fibrosis were common findings (Fig. 3). Anti-factor VIII and CD34 were stained in endothelial cells only and vimentin were stained in spindle shaped cells as well as endothelial cell (Fig. 4). CLA was expressed in lymphocytic infiltrate in the epidermis and dermis of PKS, whereas it was negative in KS (Fig. 5). PCR for HHV 8 showed negative result, but it was positive in all the specimens of KS.

#### **Treatments and prognosis**

The patients with Mali-type were treated with aspirin, coumadin, and/or pentoxifyllin as well as supportive care, such as tight elastic stockings and leg elevation, and they showed gradual improvement. Although patient 4 with Stewart-Bluefarb syndrome showed disappearance of the lesions after excision of the adjacent hemangioma, the other patients showed persistent clinical courses despite intensive treatments including embolization of the malformed vessels.

**Table 2.** Histopathologic features of pseudo-Kaposi's sarcoma

| Patients                     | Blood vessel proliferation | Inflammation                  | Hemorrhage | Fibrosis | Hemosiderin pigment | Epidermis  |
|------------------------------|----------------------------|-------------------------------|------------|----------|---------------------|------------|
| <u>Mali type</u>             |                            |                               |            |          |                     |            |
| 1                            | +                          | +, eosinophils                | ++         | -        | -                   | normal     |
| 2                            | +                          | ++, plasma cells, eosinophils | +          | +        | -                   | acanthosis |
| 3                            | +                          | +                             | +          | -        | -                   | acanthosis |
| <u>Stewart-Bluefarb type</u> |                            |                               |            |          |                     |            |
| 1                            | ++                         | +                             | +          | +        | -                   | atrophy    |
| 2                            | +++                        | +                             | +          | +++      | +                   | acanthosis |
| 3                            | +++                        | +                             | ++         | ++       | +                   | acanthosis |
| 4                            | +                          | ++                            | +          | +        | -                   | acanthosis |

Abbrev.) -, no changes; +, ++, +++, changes ranging from mild (+) to marked (+++).

**Fig. 3.** (A & B) Acanthotic epidermis, mild infiltrate of inflammatory cells in the upper dermis, and fibrosis were common findings of PKS (H & E, A  $\times$  100, B  $\times$  200). (C) Numerous vascular proliferation, vascular slits, and spindle cells in KS (H & E,  $\times$  200).

Fig. 4. (A) Anti-CD34 were stained in endothelial cells only ( $\times 100$ ) and (B) vimentin were stained in spindle shaped cells as well as endothelial cell ( $\times 100$ ).

Fig. 5. (A & B) CLA was expressed in lymphocytic infiltrate in the epidermis and dermis of PKS (A,  $\times 100$ , B,  $\times 200$ ). (C) CLA was negative in KS ( $\times 100$ ).

## DISCUSSION

KS is a proliferative vascular lesion that may appear in normal or immunocompromised hosts. Al-

though the diagnosis of typical KS is easy, clinical and/or histological simulators of this condition exist that may pose problems of differential diagnosis. The disease that most closely mimics KS, both

clinically and histologically, is PKS, also known as acroangiodermatitis of the feet (including the Mali and Stewart-Bluefarb syndromes)<sup>7</sup>. They manifest clinically as angiomatous papules and plaques, usually on the legs. The prognosis and the therapy differ essentially in both diseases and, therefore, the differential diagnosis is important. Although Kanitakis et al<sup>7</sup> suggested that CD34 expression helps in differential diagnosis between PKS and KS, our previous studies showed equivocal expression of CD34 in dermal spindle cell of KS. Therefore, the development of new tool to differentiate between these two diseases is necessary.

Histopathologically, pseudo-Kaposi sarcoma displays an increased number of thick-walled dermal vessels lined by plump endothelial cells, extravasation of erythrocytes, and deposits of hemosiderin<sup>6,8</sup>. In Mali's variant, the histopathological changes are mostly in the upper half of the dermis, whereas in the Stewart-Bluefarb syndrome the entire dermis may be affected<sup>6</sup>. In our study, although specific histopathological differences were absent in both types, proliferation of blood vessels, fibrosis, hemosiderin pigment, and epidermal thickening were more prominent in Stewart-Bluefarb type. In Stewart-Bluefarb type, congenital AV malformation, AV fistulae, Klippel-Trenaunay syndrome, and capillary hemangioma were primary disorders. The Klippel-Trenaunay syndrome is a condition characterized by limb hypertrophy, capillary vascular malformations, and varicose veins<sup>9</sup>. Secondary cutaneous manifestations include eczema, hyperhidrosis, atrophy, ulcerations, and cellulitis of the skin<sup>10</sup>. PKS is an infrequently reported skin lesion found in association with Klippel-Trenaunay syndrome. Only two cases of PKS associated with Klippel-Trenaunay syndrome were described in English literatures<sup>9,11</sup>. Interestingly, our study includes a case of this association.

The pathogenesis of PKS is poorly understood. It has been suggested that retrograde blood flow, with high venous and capillary pressure and edema, may stimulate proliferation of endothelial cells and fibroblasts<sup>6,12</sup>. As a circulatory compensation for the hypoxia, either congenital dysplastic AV junctions are dilated (Stewart-Bluefarb type) or new pathologic vessels are built (Mali type), resulting from progressive vascular and endothelial proliferation.<sup>12</sup> Although Rao et al<sup>8</sup> described that the lesions of PKS are clinically discrete and well-cir-

cumscribed, and thus differ from stasis dermatitis, Yi and Lee<sup>4</sup> presented a patient with PKS as a variant of stasis dermatitis. We also regard PKS as a clinical variant of stasis dermatitis, because reticulated brown-purple patches were seen, especially in Mali type of our cases.

Immunohistochemical staining for CD34, factor VIII, vimentin and CLA revealed that CD34 and factor VIII were stained in endothelial cell only and vimentin were stained in dermal spindle cells as well as endothelial cells. In PKS, CLA was stained in infiltrated lymphocytes in epidermis and dermis, whereas reactivity of CLA was absent in KS.

Memory T cells that infiltrate the skin express an unique skin-homing receptor called CLA, a carbohydrate epitope that facilitates the targeting of T cells to inflamed skin<sup>13</sup>. CLA defined by HECA-452 monoclonal antibody has been proposed as the novel skin-homing receptors of infiltrative lymphocytes in atopic dermatitis, lichen planus, erythema multiforme, drug eruption, and graft-versus-host disease (GVHD)<sup>14,15</sup>. CLA expression develops peripherally as a consequence of antigenic stimulation<sup>14</sup>. Picker et al<sup>14</sup> reported that only 5% of lymphocytes within the T-cell areas expressed CLA in extracutaneous sites, whereas in inflammatory skin lesions 85% of them expressed CLA. CLA is expressed in the epidermotropic malignant T cells of mycosis fungoides, but not in extracutaneous T lineage lymphomas<sup>16</sup>. The significance of this tissue-selective expression is revealed by the observations that (1) in the setting of chronic inflammation, the vascular adhesion molecule, E-selectin, is preferentially observed at cutaneous sites, (2) the CLA+ T cell subset specifically binds this selectin, and (3) CLA is the major T cell ligand for E-selectin.<sup>17,18</sup> CLA on T cells and E-selectin on inflamed dermal endothelium constitute a receptor-ligand pair that selectively mediates T cell extravasation at cutaneous sites of chronic inflammation.<sup>14</sup> Local microenvironment may play a critical role in the distribution of immune resources by modulating the expression and function of CLA<sup>14</sup>. Repeated activation in skin or skin-associated peripheral lymph nodes may act to reinforce CLA expression on T cells functionally-associated with skin, and thus enhance the functional efficiency of these cells by preferentially focusing their recirculation to the skin or related sites<sup>14</sup>. It might indicate that the different expression of CLA between PKS

and KS be ascribed to specificity of the infiltrated lymphocytes. In PKS, disease-related lymphocytes might be infiltrated, whereas in KS infiltrated lymphocytes might be bystander T cells. We suggest that the frequent extracutaneous manifestations of KS can be explained by the previous report that the expression of CLA in extracutaneous was much lower than in the skin<sup>14</sup>. Our study may confirm this elucidation and CLA may be a tool in the differential diagnosis between PKS and KS. In addition, the detection of HHV8 by PCR may be a useful tool, because HHV8 is negative in PKS, but positive in KS.

PKS can be differentiated from KS by the regularity of the vessels, the lack of vascular slits, apoptotic endothelial cells and spindle cells, the absence of vessels tending to partially surround pre-existing normal blood vessels or cutaneous annexae (promontory sign), and the relative paucity of the inflammatory cell infiltrate<sup>6,19</sup>. The presence of more edema, extravasated erythrocytes, and hemosiderin, may also help in differential diagnosis<sup>20</sup>.

We suggest that detection of HHV 8 by PCR and immunohistochemical study for CLA may be effective tools in the differential diagnosis between them.

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