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# D2-40 negative pyogenic granuloma-like Kaposi's sarcoma: Diagnostic features and histogenetic hypothesis of an uncommon skin tumor in HIV-negative patients

D. Cabibi [a], A.G. Giannone [a,*], C. Guarnotta [a], O. Schillaci [b], V. Franco [a]

[a] Anatomic Pathology, Department of Sciences for Promotion of Health and Mother and Child Care, University of Palermo, Palermo, Italy
[b] Servizio di Anatomia Patologica, Dipartimento Oncologico di III livello, La Maddalena Casa di Cura di Alta Specialità, Palermo, Italy

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ABSTRACT

Pyogenic granuloma-like Kaposi's sarcoma (PGLKS) is a recently described skin tumor showing features both of pyogenic granuloma (PG) and Kaposi's sarcoma (KS). The differential diagnosis is often challenging. We reviewed a series of 50 PG and 23 Ks located on distal extremities with the aid of an immunohistochemical panel comprising CD34, CD31, FVIII, SMA, D2-40, HHV8.

After revision, 6/50 PG lesions previously diagnosed as PG, showed positive immunostaining for LNA1-HHV8 and focal positivity for CD31 and FVIII in the endothelial cells of the proliferating vessels, with some SMA positive pericytes. D2-40, a marker of lymphatic endothelium positive in KS, stained negatively. These lesions were renamed PGLKS. Of note, in our series, PGLKS represented the only form of KS localized in the hand; all the patients were HIV-negative, older than PG patients, with a prevalence for male gender.

PGLKS and PG need a different management and a follow-up is advisable for PGLKS, as for the other variants of KS. To date, D2-40 negative immunostaining has not yet been reported in PGLKS and should not lead to a misdiagnosis of PG. The morphological similarities with PG and the immunohistochemical findings, showing a defective phenotype of the neoplastic cells, suggest a histogenetic hypothesis in which D2-40 negative PGLKS could represent an early stage of HHV8 infection of a pre-existing PG, whose vessels loose progressively their blood vascular markers but have not still acquired the lymphatic ones.



## Introduction

Pyogenic granuloma-like Kaposi's sarcoma (PGLKS) is a recently described skin tumor showing features both of pyogenic granuloma (PG) and Kaposi's sarcoma (KS). It was initially named "Kaposi's sarcoma-like pyogenic granuloma" (KSLPG) and considered benign [1,2]. Due to the clinical course and to the presence of human herpesvirus-8 (HHV-8) DNA, it is now considered a distinct clinic-pathologic variant of KS and was thus renamed "pyogenic granuloma-like Kaposi's sarcoma".

The histological features of PGKS have been recently reported by some authors [3–5]. Although it represents an uncommon skin lesion, it needs to be recognized in order to avoid diagnostic pitfalls. In daily practice, the differential diagnosis with PG is often challenging. Both lesions are commonly located on distal extremities and occur as solitary nodule with an exophytic silhouette, covered by thickened and ulcerated epidermis with a typical collarette; they are characterized by a well-circumscribed, lobular proliferation of capillary-sized vessels with fibrous septa between the lobules.

The exact origin of the neoplastic endothelial cells (blood vs lymphatic) in KS has been debated [6–8].

Due to the rarity of PGLKS and to its recent recognition as a distinct entity, we reviewed our series of acral PG and KS to better understand this lesion and its real incidence among the acral nodular lesions with features of PG. Moreover, with the aid of an immunohistochemical panel, comprising D2-40 antibody, a highly sensitive and specific marker of lymphatic endothelium [6,9], we tried to better understand the histogenesis of this rare variant of KS.

## Materials and methods

We retrospectively reviewed all the solitary acral nodular lesions that came to our observation and were diagnosed as PG

* Corresponding author at: Dipartimento di Scienze per la Promozione della Salute e Materno-Infantile "G. D'Alessandro", Anatomia Patologica, A.O.U. Policlinico "P. Giaccone", Via del Vespro, 129, 90127 Palermo, Italy. Tel.: +39 0916553515; fax: +39 0916553549.
*E-mail address:* aggianno@alice.it (A.G. Giannone).

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in the period between 2007 and 2013. They consisted of 50 cases. By comparison, we reviewed all the cases previously diagnosed as KS in acral location in the same period, consisting of 23 cases.

The surgical specimens were fixed in 10% neutral buffered formalin and routinely processed. Paraffin-embedded blocks were sectioned (3 μm thickness) and stained with hematoxylin and eosin.

Immunohistochemical stains were carried out with BenchMark XT automated slide staining system (Ventana Medical Systems, Tucson, AZ) according to the manufacturer's instructions, using the following primary antibodies: CD31 (clone JC70), CD34 (clone QBEND/10), Factor VIII (FVIII) (polyclonal), α-smooth muscle actin (SMA) (clone 1A4), Podoplanin-1 (clone D2-40) and anti-latent nuclear antigen 1 (LNA-1) for HHV-8 (Clone 13B10). For all the immunohistochemical stains, 3,3′-diaminobenzidine kit was used as chromogen. As positive internal control, we used endothelial cells for CD31, CD34 and FVIII antibodies; lymphatic endothelial cells for D2-40; smooth muscle cells of well-formed blood vessels for SMA. Negative controls without primary antibodies were included in each immunohistochemical run.

The slides were finally observed on Leica DM2000 microscope, microphotographs were obtained using a Leica DFC320 Camera.

## Results

The 50 acral nodular lesions previously diagnosed as PG were located on the hand (40/50) and on the foot (10/50). Overall, 44/50 showed classic histological features of PG. The patients with diagnosis of PG were predominantly young adults, with 75% of them younger than 60 years (male to female ratio = 1:1). The lesions were polypoid, red–brown in color, ranging from 0.5 to 2.4 cm in diameter. The surface was often ulcerated and easily bleeding. Histologically, they showed a lobular pattern with fibrous septa intersecting the lesion. Each lobule was composed of aggregations of capillaries and venules lined by plump endothelial cells, arising from a feeding central vessel. Most lesions had entirely re-epithelized, and the epidermis formed a collarette of hyperplastic epithelium at the periphery, partially embracing the lesion. The vessels were lined by endothelial cells, immunohistochemically positive for CD31, CD34 and FVIII, and by an external layer of SMA-positive pericytes.

Noteworthy, 6/50 (12%) cases showed some histological and clinical features both of pyogenic granuloma and of the classic form of Kaposi Sarcoma (nodular stage). Five of them were men and one was a woman. All the patients were older than the PG patients (mean age > 60 years), negative for human immunodeficiency virus (HIV), and they presented solitary, reddish nodules of the skin (diameter ranging from 0.8 to 4 cm) localized in the extremities. Three cases were located on the hand, representing 5% (3/40) of the previously diagnosed PGs of the hand; three were located on the foot, representing 33% (3/10) of the previously diagnosed PGs of the foot. Histologically, they showed many features overlapping with PG. Fig. 1 shows two different cases of this group. The lesions were polypoid or pedunculated, with ulcerated surface, inflammation, edema and hemorrhage. The epidermis formed a collarette of hyperplastic epithelium at the periphery. The lesions showed aggregations of capillaries and venules lined by plump endothelial cells and the lumen filled by erythrocytes. A feeding central vessel was often present [Fig. 1]. Fibrous septa intersected the lesion. A careful observation evidenced very scant spindle cells areas, difficult to detect on hematoxylin–eosin stain and lacking a true sarcomatous appearance. These areas were absent in one of the six cases.

Some of the vessels showed positivity for SMA in the pericytes and for CD31, CD34 and FVIII in endothelial cells, as PG. Most of them, with dilated lumen filled of red cells, showed only focal positivity for CD31, FVIII in the endothelial cells [Fig. 2a and b] though positivity for CD34 was kept (Fig. 2c and d). Only a few vessels retained a focal outlining of SMA-positive pericytes [Fig. 2e]. The scanty spindle cells areas were positive for CD31, FVIII, a-SMA and CD34 [Fig. 2d]. Both the endothelial cells and the scanty spindle cells stained negatively for D2-40 [Fig. 3a]. Only normal small pre-existing lymphatic vessels, in the periphery of the lesion, were D2-40 positive and were used as internal control [Fig. 3a]. Immunohistochemistry revealed nuclear positivity for LNA1-HHV8, as in the nodular stage of classic KS, but confined to the endothelial cells of the vessels [Fig. 3b].

Nested polymerase chain reaction, assayed in duplicate on paraffin-embedded samples, confirmed the presence of HHV-8 DNA in all the six specimens. On the basis of the above-reported histological and immunohistochemical features, according to the literature [3], we renamed these cases "PGLKS".

By comparison, we reviewed all the cases with classic KS in acral location observed in the same period. They consisted of 23 cases, all of them located on the on foot. No cases of classic KS were detected on the hand. The KS patients were predominantly elderly HIV-negative men (age > 60 ages). They showed a nodular silhouette and consisted of a proliferation of spindle cells staining positively for CD31, CD34, D2-40 [Fig. 3c] and HHV8. Unlike PG and PGLKS, mature blood vessels, formed by CD31, FVIII positive, D2-40 negative endothelial cells and by α-SMA positive pericytes, were absent.

## Discussion

PGLKS is a rare KS variant. Until 2002, only few items had been reported in the literature, both of them reporting this lesion as a variant of PG, and as such considered benign [1,2].

Due to the HHV8 detection both in peripheral blood and in the tissue, it was considered a KS variant [3–5].

In our case series, we found that 6/50 acral nodular lesions (12%) were forwarded to us with the clinical suspicion of PG, were PGLKS.

Noteworthy, the hand was the most frequent site of localization of PG (40/50 cases of our PG casuistry), and no classical nodular KS cases were evidenced in this location. After the review, three PGLKS cases, previously diagnosed as PG, were located on the hand, representing 100% of KS in this site. PG is a benign vascular tumor that usually occurs as a single lesion, mainly in the extremities of young people, showing a lobular proliferation of capillaries and venules with a feeding vessel and an epidermal collarette of hyperplastic adnexal epithelium at the periphery [10,11]. On the contrary, classic KS is frequently observed in elderly men and usually manifests with multiple vascular nodules on the skin and other organs.

In our casuistry and in the literature, patients with PGLKS were older than sixty-year-old, HIV negative men, and presented a solitary skin red nodule in acral location.

Like PG, PGLKS showed an exophytic, polipoid-like silhouette, covered by thickened and ulcerated epidermis forming a collarette at the base and a well-circumscribed, lobular proliferation of well-formed capillaries with a feeding vessel and fibrous septa.

The presence of solid areas of spindle cells can be difficult to recognize because they are scant and often obscured by severe inflammation, edema and hemorrhage. PG shows mature blood vessels formed by endothelial cell positive for CD31, CD34 and F-VIII and pericytes positive for SMA. In KS, mature blood vessels are scanty and the well evident spindle cells areas are positive for D2-40, CD31, CD34, and HHV8 and negative for FVIII and SMA immunostaining.

Recently, in PGLKS, we reported the presence of areas of mature vessels with immunohistochemical staining as PG vessels, together