

Primary Classic Kaposi's Sarcoma Of Lymph Nodes In Ultrasound Resembling Lymphatic Metastases Of A Malignant Tumor And Successful First-Line Therapy With Ipilimumab

Keywords: Classic Kaposi's sarcoma; Primary nodal; Lymph nodes; Ultrasound; Immune checkpoint inhibitor; Ipilimumab

Abstract

We report on a 71-year-old patient with a classic, primary Kaposi's sarcoma of the lymph nodes. He presented with an inguinal lymphadenopathy. An ultrasound examination showed suspicious lesions (oval lymph nodes with a single, round, homogeneous hypoechoic structure with peripheral and diffuse vascularization), yet typical sonomorphological criteria for lymph node metastases of a solid malignant tumor such as melanoma (round lymph nodes with a round hypoechoic area that often contains hyperechoic structures due to necrosis and a peripheral vascularization) were not fully met. Nevertheless, due to the suspicious findings, inguinal lymph nodes were extirpated. Histologically, there were formations of a malignant tumor that led to the diagnosis of a nodal Kaposi's sarcoma. Skin examinations, HIV testing and imaging procedures presented no pathological findings. A therapy with ipilimumab (3mg/kg every three weeks for four times) was initiated, which resulted in durable tumor control.

Sonomorphological patterns for Kaposi's sarcoma of the lymph nodes are not yet defined. We report on this case to describe the specific sonomorphological structures in our patient as a first step towards establishing sonomorphological criteria for nodal Kaposi's sarcoma. Furthermore, this is the first case to report on a successful first-line therapy with the immune checkpoint inhibitor ipilimumab in classical Kaposi's sarcoma.

Abbreviations

KS: Kaposi's Sarcoma

Introduction

Kaposi's Sarcoma (KS) is a rare, malignant, angioproliferative, multifocal systemic disease. Angioproliferative tumors can occur in the skin, mucous membranes, lymph nodes and other organs. It has been classified into four sub-types: classic (typically presents in middle or old age in Mediterranean or eastern European men), endemic (in indigenous Africans), iatrogenic (associated with immunosuppressive therapy) and AIDS-associated KS (Table 1). In about 90% of cases it is associated to human herpes virus-8 (HHV-8), also known as KS-Associated Herpes Virus (KSHV) [1-3]. In this

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Case Report



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paper we will focus on classic KS since our patient suffered from a rare subtype of it: a primary nodal classic KS.

Usually, the suspected diagnosis is based upon the appearance of skin lesions that vary from reddish blue to dark brown macules, plaques or nodules. KS can be confirmed by histological examination of the affected tissue, which typically shows evidence of angiogenesis with thin-walled cleft-shaped vascular spaces, inflammation (lymphocytes, plasma cells and macrophages) and spindle cell proliferation [4-6]. In nodular lesions, tumors are more solid and there are large fascicles of spindle-shaped endothelial cells with fewer and more compact vascular slits. The mononuclear cellular infiltrate decreases [4-6]. The histological diagnosis of nodal involvement is complicated. At early stages there are similarities to reactive processes. Only later in the course of the disease do spindle-shaped cells become prominent [7]. Cells of the vascular structures and spindle cells stain for endothelial markers such as CD31, CD34 and ERG as well as for D2-40/Podoplanin. Immunohistochemical staining can be done to detect the presence of HHV-8-LNA (latent nuclear antigen) within the tumor cells or polymerase chain reaction can be performed to detect HHV-8-DNA [6, 8]. Kaposi sarcoma is the only vascular tumor with positivity for HHV-8.

An important aspect during initial examination is the palpation of lymph nodes to check for nodal involvement. Additionally, an ultrasound of lymph nodes should be done to rule out nodal spreading. To our best knowledge, there are no published sonomorphological criteria of affected lymph nodes to date.

Further screening for distant organ involvement is dependent on the subtype. In the case of asymptomatic patients with classic KS, a radiographic evaluation is not normally needed due to the low frequency of radiographically evident metastatic disease [9]. Patients with gastrointestinal symptoms (e.g. bleeding, diarrhea, protein-losing enteropathy, perforation) should undergo an endoscopy to check for visceral mucosal involvement [9-11]. A staging system for classic KS, proposed by Mitsuyasu and Groopman (1998), is commonly used. The disease is grouped into stage I-IV based upon disease distribution and clinical symptoms (Table 1).

Table 1: Four variants of Kaposi's sarcoma. We focus on classic Kaposi's sarcoma (primarily nodal) in this paper.

Types of Kaposi's sarcoma	Risk group	Affected organs	Staging systems	Treatments
Classic	Elderly Mediterranean/eastern European men	- mainly skin/mucous membranes - seldom lymphatic tissue (also as primary nodal KS) or internal organs	Mitsuyasu and Groopman: Stage I: < 10 cutaneous lesions/ one anatomic region Stage II: > 10 cutaneous lesions/ > 1 anatomic region Stage III: visceral lesions only Stage IV: cutaneous and visceral lesions Stage IV A: without general symptoms Stage IV B: with fever and/or weight loss	Local: excision, radiation therapy Topic: retinoids, imiquimod, nicotine patches, rapamycin and beta blockers Systemic: - chemotherapy (e.g. pegylated liposomal doxorubicin or paclitaxel, docetaxel, bleomycin, vinblastine, vincristine, gemcitabine) - immunomodulatory agents as interferon alpha and thalidomide
Endemic	Indigenous African children and adults	-mainly skin/mucous membranes -seldom lymphatic tissue or internal organs	Mitsuyasu and Groopman: see above	Local: excision, radiation therapy Topic: retinoids, imiquimod, nicotine patches, rapamycin and beta blockers Systemic: chemotherapy (e.g. pegylated liposomal doxorubicin or paclitaxel, docetaxel, bleomycin, vinblastine, vincristine, gemcitabine) immunomodulatory agents as interferon alpha and thalidomide
Iatrogenic/ immunosuppressive	Related to immunosuppressive therapy / immunosuppressive diseases	-mainly skin/mucous membranes -seldom lymphatic tissue or internal organs	Mitsuyasu and Groopman: see above	Local: excision, radiation therapy Topic: retinoids, imiquimod, nicotine patches, rapamycin and beta blockers Systemic: reconstitution of the immune system
AIDS-associated	HIV positive patients	-mainly skin/mucous membranes -seldom lymphatic tissue or internal organs	AIDS Clinical Trials Group (ACTG) staging criteria (including tumor extent, systemic symptoms and immune status)	Local: excision, radiation therapy Topic: retinoids, imiquimod, nicotine patches, rapamycin and beta blockers Systemic: HAART

The course of the disease is dependent on the subtype. Classic Kaposi's sarcoma mostly has a chronic, indolent course and rarely impacts survival. Sometimes, however, it has an acute onset with rapid progression or a previously indolent disease can undergo sudden worsening, causing significant morbidity and mortality [12-14]. In 5-20% of cases there is a mucosal and/or organic involvement [15].

Since there is no treatment to cure classic KS, the treatment generally aims to achieve symptom palliation, improving function and delaying or preventing progression [9]. Local therapy includes excision even though local recurrences are common [15]. KS is radiosensitive, so radiation therapy of cutaneous tumors is a good option. Topical therapy with retinoids, imiquimod, nicotine patches, rapamycin and beta blockers is only marginally efficient [9]. Systemic treatments such as chemotherapy are used in cases of rapid progression or multilocal disease. Standard treatment includes pegylated liposomal doxorubicin or paclitaxel, docetaxel, bleomycin, vinblastine, vincristine, gemcitabine, and etoposide as second line [9,16,17]. However, chemotherapy is mostly palliative. Immunomodulatory agents as interferon alpha and immunomodulatory imide drugs (as thalidomide) have been used in single cases with variable efficacy [16,18]. Recently published case reports indicate that a therapy with anti-PD-1 agents might be a new and successful therapy option [17,19,20].

Case Report

We report on a 71-year-old patient with a classic, primary Kaposi's sarcoma of the lymph nodes. Due to palpable inguinal lymphadenopathy the patient presented at the clinic. On ultrasound, lymph nodes presented suspicious being hyperechoic, oval shaped with a single, round, homogeneous hypoechoic structure. The hyperechoic structure showed a strong peripheral and diffuse vascular pattern (Figure 1). These sonographic findings, albeit not entirely typical, resembled those of lymph node metastases which regularly present as hyperechoic, round shaped lymph nodes with a round, nonhomogeneous hypoechoic area due to necrotic parts of the metastases and a mainly peripheral vascularization (Figure 2). However, due to missing hyperechoic parts within the round, hypoechoic structure and a strong diffuse vascularization, criteria for lymph node metastases were only partially met. Furthermore, the bilateral appearance of suspicious lymph nodes at the same time was not impossible but uncommon for metastases. The presenting lymph nodes seemed to be a mixture of metastases (due to the hypoechoic structure with peripheral perfusion) and reactive lymph nodes (due to the additional, strong diffuse perfusion). Due to these ultrasound findings, imaging was extended. A CT showed soft-tissue masses, unknown pulmonary lesions and suspect inguinal, iliac and axillary lymph nodes. A bilateral extirpation of inguinal lymph nodes was done. Histologically, there were formations of a malignant tumor with siderosis and a mesenchymal proliferation of atypical spindle-shaped endothelial cells (Figure 3 and 4). The vascular markers CD34, CD31, D2-40/Podoplanin as well as HHV8 showed a positive result

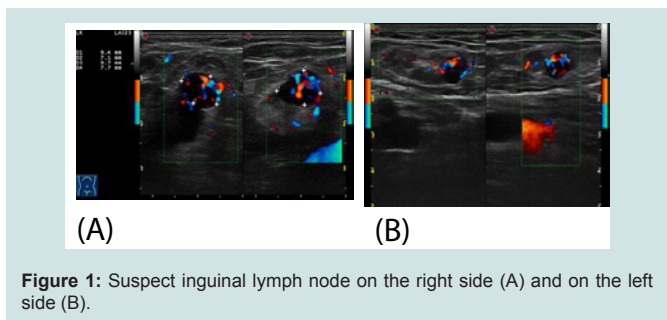


Figure 1: Suspect inguinal lymph node on the right side (A) and on the left side (B).

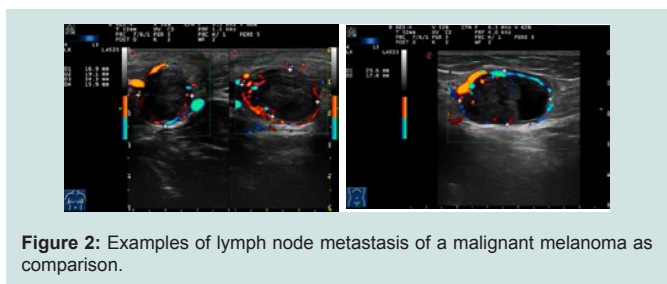


Figure 2: Examples of lymph node metastasis of a malignant melanoma as comparison.

in the immunohistochemical staining (Figure 5 and 6). Histologically, the diagnosis of a Kaposi's sarcoma was rendered. Skin examinations, HIV testing and blood tests that were done to rule out other organ manifestations and immunodeficiency were without pathological findings. An esophagogastroduodenoscopy was performed due to intermitting sickness. A gastritis was diagnosed but there was no sign of mucosal tumor lesions. The patient also had not received any immunosuppressive therapy. Therefore he was diagnosed with a classic primary Kaposi's sarcoma of the lymph nodes, an exceptionally rare sub-type of classic KS since in most cases the diagnosis is rendered due to skin lesions (i.e. not primarily nodal). A therapy with ipilimumab (3mg/kg body weight, 4 cycles, every 3 weeks) was given from June to August 2014. It was well tolerated except for a transient hypophysitis as an immune-related adverse event. The last staging was done in 2019 and showed ongoing regressive lymph nodes and no other pathological findings. The soft tissue masses that were apparent upon primary staging had also fully resolved after therapy with ipilimumab. Thus no further therapy was initiated up to now.

Discussion

The main and so far undescribed aspects of this case report are sonomorphological criteria in KS of the lymph nodes and the therapy with the immune checkpoint inhibitor ipilimumab in classic KS.

The use of ultrasound as a non-invasive imaging procedure is performed in several skin diseases [21]. Nevertheless, there is little data available regarding the ultrasound of KS lesions. Only cutaneous lesions have been characterized a few times. Herein, the authors describe partly contradictory sonomorphological patterns. In 1993, Bogner et al. reported on skin lesions as hypoechoic, with a homogeneous structure and well-defined outlines whereas Cammarota described solid [22], nonhomogenous nodules with poorly defined outlines [23]. In 2015, Carrascosa et al. described details on the sonomorphological structure and vascularization of cutaneous tumor lesions [24]. The pattern revealed by a B-mode ultrasound was solid and hypoechoic and lesions were located in the

dermis. Nodules were more homogeneous, with regular, well-defined outlines, whereas plaques were less homogeneous with irregular edges and less well-defined outlines [24]. The color doppler showed intralesional vascularization that was prominent at the lower pole in nodules and little or absent vascularization in plaques [24].

To our best knowledge, there are no published sonomorphological criteria of affected lymph nodes in KS to date. As described, lymph nodes in our patient presented hyperechoic, oval shaped with a round, homogeneous hypoechoic structure with a peripheral and diffuse vascular pattern in ultrasound (Figure 1). Therefore, sonomorphological criteria overlap with those of e.g. melanoma metastases. Nevertheless it was not possible to determine the tumor entity by ultrasound only especially since there are no described specific sonomorphological patterns of nodal involvement in KS. Thus, it would be of great interest to include ultrasound sonography in today's routine staging for KS patients (i) in order to define in more detail lymph node involvement in KS and (ii) to establish sonomorphological criteria. This is desirable not only to improve nodal diagnostics in patients with known KS but also to evaluate therapeutic responses. Nevertheless, a histological examination of the suspect tissue is important. This case demonstrates the importance of combining ultrasound and histology to differentiate between various malignancies.



Figure 3: HE staining at 40x magnification: Mesenchymal proliferation in the upper half of the lymph node.

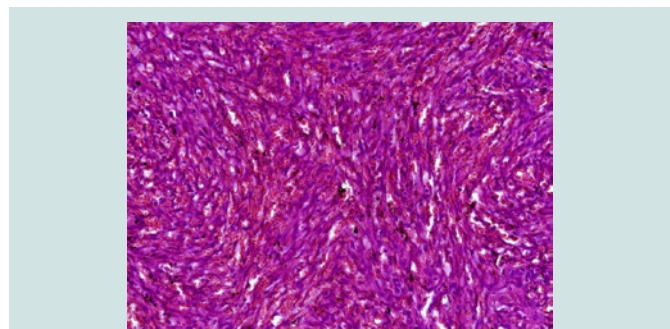


Figure 4: HE staining at 400x magnification: Mesenchymal proliferation of atypical spindle-shaped endothelial cells forming vascular spaces; extravascular erythrocytes.

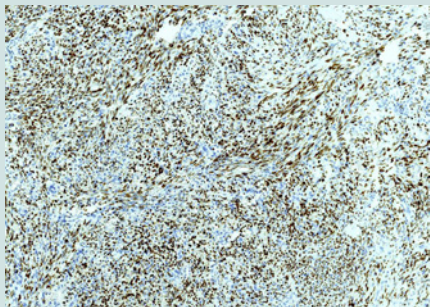


Figure 5: IHC staining at 200x magnification: HHV8 shows strong nuclear positivity.

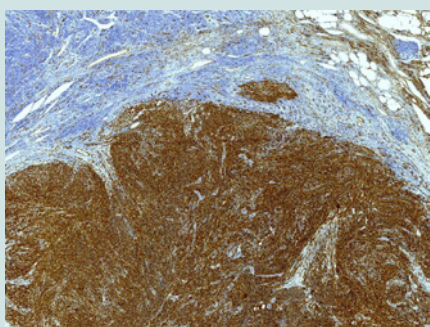


Figure 6: IHC staining at 200x magnification: CD34 shows strong cytoplasmic positivity in tumor cells.

As described above, there is no curative systemic treatment of advanced classic KS to date. Systemic chemotherapy with liposomal doxorubicin, which is used in a progressive disease, achieves mostly transient responses. A literature review of systemic treatment was done by Régnier-Rosencher et al. in 2013, who described response rates of various treatments from 43-100% but found that evidence for efficacy of any particular therapy was of low quality and a specific therapeutic strategy could not be recommended [16].

Recently published case reports strongly indicate that an anti-PD-1 therapy could be a new and successful therapy option [17,19]. Galanina et al. report a successful treatment of HIV-associated KS in nine male patients as second-line therapy [19]. Herein, six patients (67%) achieved partial (n=5) or complete remission (n=1) and the other three attained an ongoing stable disease. Delyon et al. report two cases of patients with endemic KS who were previously treated with radiation therapy and had received chemotherapy [17]. As second-line therapy they received nivolumab and a partial response was achieved for both patients. Saller et al. describe a case of advanced classic KS refractory to chemotherapy that experienced a partial response to anti-PD-1 therapy [20].

Immune checkpoint inhibition has been proven to be effective in numerous malignancies, including virally mediated tumors such as merkel-cell carcinoma (MCpV-associated) or Hodgkin's lymphoma (EBV-associated) [25,26]. Oncovirus associated tumors, including KS, seem to have a virally mediated increased expression of PD-L1 [25,27]. Contrary to these findings, higher-than-anticipated response rates were also described in virus associated tumors with low PD-L1

expression, suggesting that also the presentation of viral antigens on tumors may lead to an increased response rate to immunotherapy [26].

Our patient is the first published case of a classic, primary nodal Kaposi's sarcoma that was treated with immunotherapy. The above-mentioned case reports describe patients either suffering from classic, endemic or HIV-associated KS and receiving immunotherapy with the anti-PD-1/PD-L1-agents pembrolizumab or nivolumab. Here, we report on treatment with the CTLA-4-antibody ipilimumab that led to a stable disease (regressive soft tissue masses and axillary, iliac and inguinal lymph nodes). After a follow-up period of five years, we have no sign of disease progression in our patient. Therefore, we conclude that the therapy with ipilimumab was successful and led to a long-term stable disease. Especially since we would have expected a disease progression in this case of classic nodal KS (i.e. that is not limited to the skin) without immunotherapy. The result supports the suggestion that immunotherapy might be a promising therapy option in KS and shows that it might even lead to a long-term stable diseases or even complete response [17,19]. Furthermore, the use of immunotherapy as first-line therapy has not been reported before. Since usually used systemic therapies mostly show only a transient success, this would be a new, life-saving option for patients with advanced KS. KS in general often affects immunosuppressive patients. Chemotherapies often additionally lead to myelosuppression as a side effect. Studies with immune checkpoint inhibitors on a greater number of patients are necessary to prove efficacy. The National Cancer Institute is conducting a prospective study of combined ipilimumab and nivolumab in patients with HIV associated cancers, including Kaposi's sarcoma (Clinical-Trials.gov, Identifier: NCT02408861); final data will presumably be available at the end of 2020. The use of immunotherapy as first-line therapy is desirable in order to replace marginally effective chemotherapies.

Conclusion

Sonomorphological criteria for KS of the lymph nodes are not yet known. In our patient affected lymph nodes showed a round, homogeneous hypoechoic structure with a peripheral and diffuse vascular pattern in ultrasound leading to further diagnostics. Since nodal involvement is rare, it is desirable to publish cases like this one in order to develop a more profound and specific knowledge of sonomorphological criteria for KS of the lymph nodes and thereby improve and complement diagnostics as well as therapy evaluation.

Recently published data report on successful treatment with pembrolizumab and nivolumab in single cases of endemic and HIV-associated KS when used as second- or third-line therapy [17,19]. Considering the knowledge of immunomodulation of KS [28-30], the positive response rate to immune checkpoint blockage in other virus associated immunomodulated tumors such as merkel-cell carcinoma or Hodgkin's lymphoma and the positive response to immune checkpoint inhibitors in recently documented cases [17,19,25,26,31], it is very likely that ipilimumab has resulted in an ongoing stable disease in our patient. This case shows that immunotherapy seems to be a promising option in patients with classic, primary nodal KS. It supports the positive data about the efficacy of immunotherapy in KS due to a first-time reported follow-up of five years. Furthermore it indicates that anti-CTLA-4 therapy is a possible alternative if anti-

PD-1 therapy is not applicable.

References

1. Heinzerling L, Hartmann A, Hund M, Schuler G (2014) Drug-based tumor therapy in dermatology. Springer-Verlag Berlin/Heidelberg, Germany 162-166.
2. Gao SJ, Kingsley L, Hoover DR, Spira TJ, Rinaldo CR, et al. (1996) Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. *N Engl J Med* 335: 233-241.
3. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, et al. (1998) Sexual transmission and the natural history of human herpesvirus 8 infection. *N Engl J Med* 338: 948-954.
4. Grayson W, Pantanowitz L (2008) Histological variants of cutaneous Kaposi sarcoma. *Diagn Pathol* 3: 31.
5. Mentzel T, Knuutila S, Lamovec J (2013) Classification of tumors of soft tissue and bone (4th edn). World Health Organization 151.
6. Krown SE, Singh JC (2019) Classic Kaposi sarcoma: Epidemiology, risk factors, pathology, and molecular pathogenesis.
7. Vogt T, Brockmeyer N, Kutzner H, Schöfer H (2012) S1 - Kurzleitlinie - Angiosarkom der Haut und Kaposi-Sarkom (Update 2012). AWMF online.
8. Hbid O, Belloul L, Fajali N, Ismaili N, Duprez R, et al. (2005) Kaposi's sarcoma in Morocco: a pathological study with immunostaining for human herpesvirus-8 LNA-1. *Pathology* 37: 288-295.
9. Krown SE, Singh JC (2019) Classic Kaposi sarcoma: Clinical features, staging, diagnosis, and treatment.
10. Neff R, Kremer S, Voutsinas L, Waxman M, Mitty W, Jr. (1987) Primary Kaposi's sarcoma of the ileum presenting as massive rectal bleeding. *Am J Gastroenterol* 82: 276-277.
11. Weprin L, Zollinger R, Clausen K, Thomas FB (1982) Kaposi's sarcoma: endoscopic observations of gastric and colon involvement. *J Clin Gastroenterol* 4: 357-360.
12. Brenner B, Rakowsky E, Katz A, Gutman H, Sulkes A, et al. (1999) Tailoring treatment for classical Kaposi's sarcoma: comprehensive clinical guidelines. *Int J Oncol* 14: 1097-1102.
13. Zurrada S, Bartoli C, Nole F, Agresti R, Del Prato I, et al. (1992) Classic Kaposi's sarcoma: a review of 90 cases. *J Dermatol* 19: 548-552.
14. Di Lorenzo G, Kreuter A, Di Troilo R, Guarini A, Romano C, et al. (2008) Activity and safety of pegylated liposomal doxorubicin as first-line therapy in the treatment of non-visceral classic Kaposi's sarcoma: a multicenter study. *J Invest Dermatol* 128: 1578-1580.
15. Altmeyer P. Kaposi Sarkom. Altmeyers Enzyklopädie online.
16. Regnier-Rosencher E, Guillot B, Dupin N (2013) Treatments for classic Kaposi sarcoma: a systematic review of the literature. *J Am Acad Dermatol* 68: 313-331.
17. Delyon J, Bizot A, Battistella M, Madelaine I, Vercellino L, et al. (2018) PD-1 blockade with nivolumab in endemic Kaposi sarcoma. *Ann Oncol* 29: 1067-1069.
18. Ben M'barek L, Fardet L, Mebazaa A, Thervet E, Biet I, et al. (2007) A retrospective analysis of thalidomide therapy in non-HIV-related Kaposi's sarcoma. *Dermatology* 215: 202-205.
19. Galanina N, Goodman AM, Cohen PR, Frampton GM, Kurzrock R (2018) Successful Treatment of HIV-Associated Kaposi Sarcoma with Immune Checkpoint Blockade. *Cancer Immunol Res* 6: 1129-1135.
20. Saller J, Walko CM, Millis SZ, Henderson-Jackson E, Makanji R, et al. (2018) Response to Checkpoint Inhibitor Therapy in Advanced Classic Kaposi Sarcoma: A Case Report and Immunogenomic Study. *J Natl Compr Canc Netw* 16: 797-800.
21. Wortsman X (2012) Common applications of dermatologic sonography. *J Ultrasound Med* 31: 97-111.
22. Bogner JR, Zietz C, Held M, Spathling S, Sandor P, et al. (1993) Ultrasound as a tool to evaluate remission of cutaneous Kaposi's sarcoma. *AIDS* 7: 1081-1085.
23. Cammarota T (1998) *Ecografia in Dermatologia*. Poletto Editore, Milano.
24. Carrascosa R, Alfageme F, Roustan G, Suarez MD (2016) Skin Ultrasound in Kaposi Sarcoma. *Actas Dermosifiliogr* 107: e19-e22.
25. Hu B, Jacobs R, Ghosh N (2018) Checkpoint Inhibitors Hodgkin Lymphoma and Non-Hodgkin Lymphoma. *Curr Hematol Malig Rep* 13: 43-54.
26. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, et al. (2016) PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med* 374: 2542-2552.
27. Paydas S, Bagir EK, Deveci MA, Gonlusen G (2016) Clinical and prognostic significance of PD-1 and PD-L1 expression in sarcomas. *Med Oncol* 33: 93.
28. Amodio E, Goedert JJ, Barozzi P, Riva G, Firenze A, et al. (2011) Differences in Kaposi sarcoma-associated herpesvirus-specific and herpesvirus-non-specific immune responses in classic Kaposi sarcoma cases and matched controls in Sicily. *Cancer Sci* 102: 1769-1773.
29. Beldi-Ferchiou A, Lambert M, Dogniaux S, Vely F, Vivier E, et al. (2016) PD-1 mediates functional exhaustion of activated NK cells in patients with Kaposi sarcoma. *Oncotarget* 7: 72961-72977.
30. Roshan R, Labo N, Trivett M, Miley W, Marshall V, et al. (2017) T-cell responses to KSHV infection: a systematic approach. *Oncotarget* 8: 109402-109416.
31. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, et al. (2016) Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol* 17: 1374-1385.