Journal of Pakistan Association of Dermatologists. 2023;**33(4)**:1685-1693.

Case Report

Progressive sarcoma Kaposi after COVID-19

Yu.V. Molochkova, M.G. Kartashova, M.K. Monaenkova

Department of Dermatology, Moscow Regional Research and Clinical Institute ("MONIKI") Moscow, Russia, st. Shchepkina 61/2, 129110, Moscow, 129110.

Abstract This article deals with the sarcoma Kaposi worsening after severe coronavirus infection. After 2 years of sarcoma Kaposi remission a 70-year-old male HIV-negative patient noted new violaceous skin nodules. A few months before he recovered from COVID-19. We present the case and review of literature.

Key words
Sarcoma Kaposi; COVID-19; Herpes virus 8: SARS-CoV-2: Immunosuppression.

Introduction

Examination of the upper extremities (wrist, forearm, shoulder), lower extremities (hip, shin) revealed scattered solitary hemispherical papules 0.8-1.0 cm in diameter, with clear boundaries, dark brown to purple in color, with smooth surface, merging into plaques with convex surface up to 2.0 cm in diameter in some places. The mucous membranes are rash-free. Peripheral lymphatic nodes were not enlarged.

Kaposi sarcoma (KS) is a malignant tumour that has a vascular origin and is usually human herpes virus type 8 (HHV-8) associated.[1] Herpes virus type 8 (HHV-8) belongs to the Gammaherpesvirus subfamily, Radinovirus genus.[2] The phase of the HHV-8 life cycle depends on the expression of certain genes: either lytic (gene T1.1, etc.) or latent (gene for LANA-1).[3] The tumorigenic nature of the virus is due to its ability to fuse the LANA-1 protein responsible for inhibiting p53 protein in the apoptosis of the infected cell and the viral Interleukin 6, responsible for viral angiogenesis, evasion of the host immune response, and viral proliferation.[3] Currently, four major types of KS are recognized clinically, the AIDS-associated type, the iatrogenic type caused by solid organ transplants, the endemic type - prevalent in sub-Saharan Africa, among patients without HIV infection, and the idiopathic (classic) type.[1] In recent years, a fifth subtype of KS, common in homosexual men without HIV infection (the so-called MSM-type), has been separately identified.[17] Regardless of the type of KS, clinically, the pathological elements of KS occurring on the skin and mucosa have a false polymorphism linked to the sequential evolution of the elements. Thus, in the early stages, the process is represented by patches (spot stage), which subsequently transform first into papules (plaque stage) and then into tumour nodules (tumour stage). The colour of the lesions varies from a pinkish to purplish-purple colour. The lesions may occur in isolation or may have a tendency to coalesce into plaques.[24] When the elements are traumatized, they may become ulcerated, which is more common when the process is localized to the skin of the lower extremities.[19] In the WHO pathological classification of soft tissue tumours, KS is ranked among the intermediate (locally aggressive) vascular tumours.[4] Each of the three

Address for correspondence
Dr. Maria K. Monaenkova, Junior Researcher
Department of Dermatology: st. Schepkina, 61/2, Moscow, 129110.
Ph: +79150020852
Email: mar.monaenkova@gmail.com

stages of KS is characterized by distinct histological features. Thus, the spot stage is characterized by thyroid vascular lumen with thickened endothelial layer and collagen bundles, the plaque stage is characterized by spindle cell proliferation, and the nodular stage is associated with limited nodular elements and also active spindle cell proliferation.[5] Among the histological types of KS, anaplastic, lymphedematous, lymphangioma-like, lymphangiectatic, bullosa, and telangiectatic, as well as verrucosis, keloidal, micronodular, pyogenic granuloma-like, ecchymotic and intravascular types have also been documented in the field of literature, besides typical forms associated with the disease progression. The immunohistochemical screening for LANA+ protein plays an important role in the differential diagnosis of KS against other vascular lesions.[6]

AIDS-associated type A significant increase in the occurrence of KS was associated with the HIV and AIDS epidemic in the 80s and 90s in western countries, when KS became one of the first "AIDS-associated" diseases.[8] In general, the risk of developing KS in an HIV-positive patient is 3-4 times higher than in an HIV-negative patient.[9] The intensive implementation of antiretroviral therapy (ART) in the treatment of HIV infections in 1996 has led to a decrease in the KS rate, nevertheless there are regions (a number of Southern and Eastern African countries) with a high prevalence of AIDS-associated KS, which have some challenges in receiving adequate ART.[10-12] The average age of an HIV-positive patient at the onset of KS is 40 years.[14] AIDS-associated KS is characterized by the proliferation of multiple disseminated elements in the skin, often involving the visceral organs, which can eventually lead to multiple organ failure and death.[13]

Iatrogenic type Treatment with an immunosuppressant agent and various rheumatological diseases, particularly after transplantation, is another predisposing factor for the development of KS: the most commonly reported cases of KS occurring during immunosuppressive therapy after lung or kidney transplantation, with some researchers considering the elderly age of the transplant patient (over 60 years) to be an increased risk factor for the development of KS.[15] Iatrogenic KS, like AIDS-associated KS, is typically accompanied by widespread rashes affecting not only the skin but also the organs, with Buonaguro *et al*. reporting a 30% chance of death in patients with generalized rashes, with a male to female ratio of 2.3:1.[21] It is also reported that patients with iatrogenic type of KS may develop a fulminant course of the disease and may be potentially lethal.[22,23]

Endemic (African) type It is common among HIV-negative patients in the sub-Saharan African region. Three subtypes of endemic KS are separately distinguished, depending on the age, extent and type of lesions, and the rate of rash appearance: low-aggressive, locally aggressive and disseminated aggressive.[21] The more aggressive course is more common in children: the process is accompanied by polylymphoadenopathy and lesions of internal organs. In adult patients, the process is more often localized in the lower extremities and resembles the classical form of KS, with most cases being torpid without any involvement for internal organs.[1]

Classical (Idiopathic) type The disease develops more often in men of certain ethnic groups (of Eastern European and Mediterranean origin, most often in Ashkenazi Jews), with a male to female ratio of 10-15:1.[21] The average age of the patient at the onset of the disease is 60 years.[14] The idiopathic type has a torpid course, with some spontaneous regression of the lesions, affecting the lower extremities and the acral area

more frequently and rarely the face and neck.[21]

MSM type In recent years, foreign researchers have identified a fifth type of KS that specifically affects homosexual, sexually active men who are infected with HHV type 8 but not HIV-infected. The average age of the patient at disease onset is 40-50 years.[17] Clinical signs and disease progression are similar to those of classical KS, characterized by slow progression, and very rare involvement of internal organs and lymph nodes.[16,17]

Treatment

The treatment and the prognosis are determined on a case-by-case basis, depending on the type of KS, the extent of the rash, the rate of new lesions and the results of additional tests (whole body PET-CT, bronchoscopy, gastroesophageal-duodenoscopy and colonoscopy).[25] All types of KS may be treated locally (cryotherapy, radiotherapy, intradermal administration of vinblastine, vincristine, imiquimod, etc.) or systemically (pegylated liposomal doxorubicin, liposomal daunorubicin, paclitaxel, IFN-α). It is possible to limit the amount of therapy to topical treatment alone in the presence of a single, slowly progressing lesion up to 4 cm in cross-sectional diameter.[16] Indications for systemic treatment with cytostatics are rapid progression with multiple lesions and rapid growth, ulcerating lesions, and involvement of internal organs.[16]

AIDS-associated form successfully regresses with effective ART to reduce HIV load and increase CD4+ cell count.[18]

Given the widespread use of ART in recent years, an adverse phenomenon known as "immune reconstitution inflammatory syndrome" has been reported: patients receiving the first year of ART who tended to have a lower HIV viral load have had their opportunistic infections, including KS, for the first time or have progressed to existing opportunistic infections.[18] Combined use of ART and drugs used for systemic treatment of KS should prevent this condition from occurring.[16] In the case of progression of AIDS-associated KS against the background of successful ART, systemic drugs should also be used.[16]

Iatrogenic KS In case of development of KS after organ transplantation against the background of massive immunosuppressive therapy, an alternative, safer for KS, combination of immunosuppressive drugs is preferred, so, sirolimus (rapamycin), actively used in patients with KS after kidney transplantation, has shown clinical effectiveness.[19]

The medication sirolimus has both sufficient immunosuppressive and anti-tumour effects: as an mTOR inhibitor, it prevents tumour growth and has also been shown to reduce virion formation in HHV 8.[20]

A novel coronavirus infection

The potential ability of a novel coronavirus to influence oncogenesis is of particular interest. Currently, there is no unequivocal evidence of oncogenicity of coronavirus, but this issue continues to be actively discussed and studied in the scientific community. In a study of the expression of oncogenic proteins in the SARS-CoV-2 background, Ebrahimi Sadrabadi A, Bereimipour A *et al*. proved the expression of the CREB1 gene (overexpression of which leads to melanoma progression[27] and aggressive proliferation of glioblastoma cells,[28] increased formation of the mediator Caspase-3 (which has been shown to be involved in metastasis in rectal cancer,[29]), changes in the expression of actin-

binding proteins after infection with SARS-Cov-2, probably leading to the development of pancreatic cancer.[30] Alpalhão M, Ferreira JA *et al*. hypothesized the likely pathways for activation of oncogenic processes in cells when SARS-CoV-2 persists in the face of patient clinical and laboratory convalescence. Based on the suppression of pRb function by SARS-CoV-1 endoribonuclease Nsp15 and disruption of p53 suppressor protein, the authors hypothesized possible oncogenic properties of coronavirus.[31]

Policard M, Jain S in a study on the role of coronavirus in oncogenesis reported a cell division cycle disruption by the interaction of coronavirus with the Rb-E2F complex of healthy cells, potentially triggering the initiation of oncogenic cell transformation.[32] The worldwide literature reports the possibility of reactivation of some viruses against a background of temporary immunodeficiency following a COVID-19 infection. For the SARS-CoV2 pandemic, Dursun R, Temiz SA published data on an increase in the number of cases of HHV 6 following coronavirus infection, which they attributed to reactivation of HHV 6.[33] Saade A, Moratelli G *et al*. shared the report of reactivation of Epstein-Barr virus (58%), cytomegalovirus (19%) and herpes virus (12%). In a cohort (100) of patients admitted to the intensive care unit for the severe course of COVID-19, patients were quantified (by PCR) twice a week in peripheral blood for the listed viruses, and 63 of 100 were found to rise to threshold values.[34]

In this context, an important topic is the study of the course of herpes-associated skin diseases, in particular KS, in patients who have had a coronavirus infection. Cases of manifestation of KS after coronavirus infection are mainly reported in the world literature: Nasrullah A *et al* have described a clinical case of the debut of immunosuppressive Kaposi sarcoma in a 37-year-old African American man with a history of coronavirus infection: the authors suggest that the main cause of KS in this patient was a failure to receive adequate antiretroviral therapy during the pandemic.[35] Gardini G, Odolini S *et al.* also report the debut of idiopathic KS in a 61-year-old HIV-negative patient hospitalized with severe COVID-19. On in-depth examination, an enlargement of the cervical lymph nodes was found, followed by a puncture biopsy, which revealed histologically a typical Kaposi's sarcoma pattern. On rehospitalization, the patient presented with multiple purplish patches on the skin of the forearms, palms, lower extremities and palate; a CT scan revealed multiple internal organ involvement: nodules in the lung parenchyma, liver and spleen involvement, enlargement of axillary, supra- and subdiaphragmatic and inguinal lymph nodes.[36]

Magri F, *et al*. reported a clinical case of debut of KS in an 83-year-old female patient: one month after recovery from COVID-19, the patient developed purplish purple spots on the skin of the feet, and histological examination confirmed the diagnosis of Kaposi sarcoma.[37]

However, data on this topic are limited and presented only in isolated clinical observations.

We report our own clinical observation of a patient with progression of Kaposi's sarcoma after a severe coronavirus infection.

Clinical case report

We present our case report. Patient T., 70 years old, was admitted to the dermatology department Moscow Regional Research and Clinical Institute ("MONIKI") in April 2022 suffering from skin rashes on the upper and lower extremities. The patient had been diagnosed with

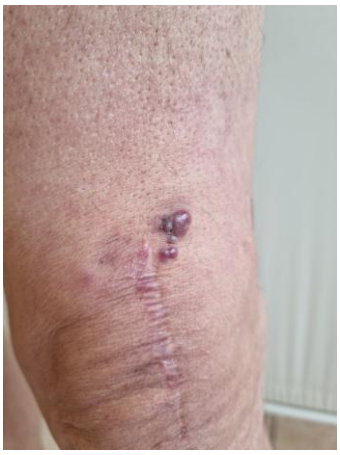

Figure 1a Dark purple rounded grouped nodes above the left knee.

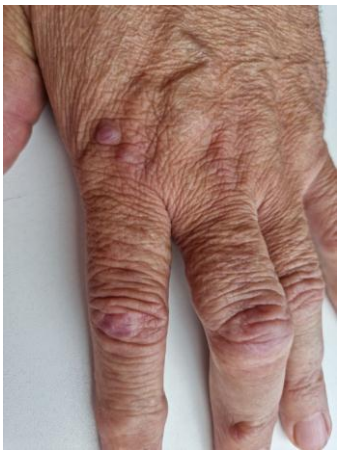

Figure1b Isolated to each other few pinkish nodes on the hand

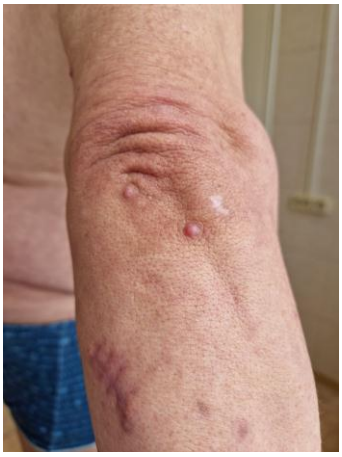

Figure 1c Sharply confined, smooth, asymptomatic pale red nodes on the right elbow.

the disease since 2018, at which time he first noted a single cherry-colored nodule on the skin of the left auricle. He went to his local health center and the mass was surgically removed. In December 2020, he had a new coronavirus infection with a 50% lung lesion (stage CT-2). For which he was treated as an inpatient, where he received systemic corticosteroid (prednisolone 40 mg) antibacterial (azithromycin 500 mg/day) and antiviral therapy. In September 2021, a cherry-red nodule of about 1 cm in size appeared on the skin of the left hand, similar to the one in 2018. He consulted a local surgeon and had the mass excised surgically. Since December 2021, noted the occurrence of multiple widespread cherry red, brown nodules on the skin of the upper and lower extremities, due to which he was admitted to our department. On admission, the general condition was satisfactory, vesicular breathing in the lungs, heart sounds rhythmic, pulse 76 bpm, BP 130/80 mm Hg, abdomen was soft and painless on palpation in all parts.

The findings of blood and urine tests were within the normal range. Biochemical analysis of blood showed cholesterol increase of 6.15 mmol/l, glucose increase of 8.8 mmol/l. Histological examination from the pathological focus: skin fragment with tumor of spindle-shaped cells and primitive vessels forming nodular structures in the dermis. Opinion: Kaposi's sarcoma, nodular stage. The patient underwent an ELISA test of blood serum to detect the level of antibodies to HHV-8 (anti-HV-8 IgG): 10.7 U/ml (reference values: 0-0.8 negative; 0.81-1.0 "grey zone"; >1.0 positive). Abdominal ultrasound revealed no evidence of involvement of the parenchymatous organs. The patient was diagnosed with Kaposi's sarcoma, idiopathic type, nodular stage on the basis of anamnestic, clinical and laboratory data and histological examination. The patient was referred to a consultant oncologist, who prescribed an additional examination, PET-CT, which did not reveal any KS foci in the internal organs. The patient is scheduled for therapy with liposomal doxorubicin.

Discussion

The pandemic coronavirus infection has led to a pronounced change in the course of chronic autoimmune and malignant diseases. The causes of this effect are under close scrutiny by researchers of different specialties. In dermatology, the effect of coronavirus infection on the course of psoriasis, squamous lichen

planus, bullous dermatoses, and several connective tissue diseases, telogen and focal alopecia.[38,39] However, the impact of coronavirus infection on malignant skin diseases is limited and reported in few clinical studies, although the effect of coronavirus infection on tumorigenesis is under investigation by specialists in various medical fields. Our attention was attracted by the work of several researchers demonstrating the possibility of reactivation of various types of herpes virus infections, including type 8 herpes virus associated with KS. Of particular interest in the course of KS in patients after coronavirus infection is the study of Leoni E, Cerati M *et al*. who observed the simultaneous presence of HHV 8 and coronavirus in a biopsy of a KS cell and justified this phenomenon by hyperactivation of the immune response against the background of coronavirus infection and acceleration of HHV 8 transition into lytic cycle.[40]

The possibility of simultaneous coexistence of the two viruses in the same environment was confirmed by Yanes, Ryan R *et al*.: by performing drainage of the pericardial cavity in connection with pericardial effusion in a COVID-19 patient, and by studying the fluid obtained, scientists detected SARS-CoV-2 and HHV-8.[41]

These findings are also supported by a laboratory study by Chen J, Dai L *et al*. who studied the effect of coronavirus proteins on HHV8-infected cells. They experimentally found that expression of specific coronavirus proteins leads to induction of lytic genes of HHV type 8, accordingly the latent cycle of HHV 8 is substituted by the lytic cycle, which leads to an increase in its number of virions in the KS nidus. This study also revealed that the angiotensin-converting enzyme receptor, which is responsible for cell attachment, was also expressed upregulated in JS tissues. In addition to the direct pathogenetic role of the coronavirus, Chen J *et al*. also discuss the role of drugs (most commonly used in COVID-19) as reactivating factors of HHV-8, in particular azithromycin, chloroquine diphosphate, hydroxychloroquine sulphate, etc.[42]

Most of the cases of the onset of coronavirus-associated KS, and only a single case of progression of KS in a patient after coronavirus disease, have been reported in the international literature. Our observation of KS progression in an immunocompetent patient after a severe course of coronavirus infection is interesting, as the exact cause of progression has not been established, but the combination of immunosuppression arising from coronavirus infection and the use of systemic HSCT in this context is likely to have been critical. Cases of progression and onset of KS on systemic steroids have been reported in the literature: patients with various autoimmune diseases who require systemic glucocorticosteroids, sometimes for life, have an increased risk of developing KS.[43-47] in our case their use was short-lived and unlikely to be a trigger for KS progression, but it is impossible to completely exclude a role of systemic HSCT, even in a low dose, especially considering the fact that their use was combined with taking azithromycin, which Chen J *et al*. consider as a contributor to the increase of HHV type 8 virions.

At the time of writing, there was one case in the available literature about the clinical progression of KS with coronavirus infection, published by Leoni E *et al*. who found the simultaneous presence of two viruses (SARS-CoV-2 and HBV-8) in a focus of KS. Remarkably, before infection with COVID-19, the patient was in remission of KS, whereas at the time of hospitalization for coronavirus infection, progression of the disease in the form of new

lesions was observed.[40] As in our case, immunosuppression after coronavirus infection in combination with antibiotics and systemic prednisolone probably played a trigger role in this case, leading to an increased number of HHV type 8 virions and worsening the course of KS. To investigate this issue, it is necessary to initiate additional studies, in particular to determine the titer of antibodies to HHV type 8 in patients with KS and to investigate the immune status in patients with the onset and progression of KS before and after a coronavirus infection.

In world practice, most oncologists have been vigilant about prescribing systemic corticosteroids to cancer patients who develop severe COVID-19. Clearly, patients are already immunosuppressed due to malignancy and ongoing antitumor therapy. This view was confirmed by scientists from China, who conducted a retrospective cohort study of 29 cancer patients with COVID-19: therapy administered for a coronavirus infection and causing immunosuppression led to an increased risk of death from COVID-19.[48] As KS is considered to be a cancerous disease, the choice of therapy for coronavirus infection must take into account the possible effect of these drugs on the further course of the malignant process. Patients receiving SSRIs/ systemic corticosteroid therapy with comorbidities should be closely monitored by oncologists and general practitioners for the timely detection of possible adverse malignancy and the timely selection of appropriate treatment options.

Conclusion

It remains to be established whether SARS-CoV-2 is one of the other factors contributing to the immunodeficiency state in which HHV 8 proliferates intensively, and KS in these patients is immunosuppressive and iatrogenic, or whether SARS-CoV-2 may have its own agents contributing to Kaposi sarcoma progression. Knowledge behind this would open up new avenues for selecting therapy for KS in that group of patients whose KS has developed after having had a COVID infection.

References

1. Cesarman E, Damania B, Krown SE, Martin J, Bower M, Whitby D. Kaposi sarcoma. Nat Rev Dis Primers. 2019;5(1):9. Published 2019 Jan 31.
2. https://ictv.global/taxonomy/taxondetails?taxnode_id=202101510
3. Katano H. Pathological Features of Kaposi's Sarcoma-Associated Herpesvirus Infection. Adv Exp Med Biol. 2018;1045:357-376.
4. Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. Pathologica. 2021;113(2):70-84.
5. Tembo R, Kaile T, Kafita D, *et al*. Detection of Human Herpes Virus 8 in Kaposi's sarcoma tissues at the University Teaching Hospital, Lusaka, Zambia. Pan Afr Med J. 2017;27:137. Published 2017 Jun 22.
6. Pereira PF, Cuzzi T, Galhardo MC. Immunohistochemical detection of the latent nuclear antigen-1 of the human herpesvirus type 8 to differentiate cutaneous epidemic Kaposi sarcoma and its histological simulators. An Bras Dermatol. 2013;88(2):243-246.
7. Denis D *et al*. A fifth subtype of Kaposi's sarcoma, classic Kaposi's sarcoma in men who have sex with men: a cohort study in Paris. J. Eur. Acad. Dermatol. Venereol. 32, 1377–1384 2018
8. Mariggiò G, Koch S, Schulz TF. Kaposi sarcoma herpesvirus pathogenesis. Philos Trans R Soc Lond B Biol Sci. 2017;372(1732):20160275.
9. Calabresi A, Ferraresi A, Festa A, *et al*. Incidence of AIDS-defining cancers and virus-related and non-virus-related non-AIDS-defining cancers among HIV-infected patients compared with the general population in a large health district of Northern Italy, 1999-2009. HIV Med. 2013;14(8):481-490.
10. Semeere AS, Busakhala N, Martin JN. Impact of antiretroviral therapy on the incidence of Kaposi's sarcoma in resource-

rich and resource-limited settings. Curr Opin Oncol. 2012;24(5):522-530.
11. Liu Z, Fang Q, Zuo J, Minhas V, Wood C, Zhang T. The world-wide incidence of Kaposi's sarcoma in the HIV/AIDS era. HIV Med. 2018;19(5):355-364.
12. Robey RC, Bower M. Facing up to the ongoing challenge of Kaposi's sarcoma. Curr Opin Infect Dis. 2015;28(1):31-40.
13. Dourmishev LA, Dourmishev AL, Palmeri D, Schwartz RA, Lukac DM. Molecular genetics of Kaposi's sarcoma-associated herpesvirus (human herpesvirus-8) epidemiology and pathogenesis. Microbiol Mol Biol Rev. 2003;67(2):175-212.
14. Grabar S, Costagliola D. Epidemiology of Kaposi's Sarcoma. Cancers (Basel). 2021;13(22):5692. Published 2021 Nov 14.
15. Cahoon EK, Linet MS, Clarke CA, Pawlish KS, Engels EA, Pfeiffer RM. Risk of Kaposi sarcoma after solid organ transplantation in the United States. Int J Cancer. 2018;143(11):2741-2748.
16. Esser S, Schöfer H, Hoffmann C, *et al*. S1 Guidelines for the Kaposi Sarcoma. J Dtsch Dermatol Ges. 2022;20(6):892-904.
17. Denis D, Seta V, Regnier-Rosencher E, *et al*. A fifth subtype of Kaposi's sarcoma, classic Kaposi's sarcoma in men who have sex with men: a cohort study in Paris. J Eur Acad Dermatol Venereol. 2018;32(8):1377-1384.
18. Achenbach CJ, Harrington RD, Dhanireddy S, Crane HM, Casper C, Kitahata MM. Paradoxical immune reconstitution inflammatory syndrome in HIV-infected patients treated with combination antiretroviral therapy after AIDS-defining opportunistic infection. Clin Infect Dis. 2012;54(3):424-433.
19. Stallone G, Schena A, Infante B, *et al*. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med. 2005;352(13):1317-1323.
20. Nichols LA, Adang LA, Kedes DH. Rapamycin blocks production of KSHV/HHV8: insights into the anti-tumor activity of an immunosuppressant drug. PLoS One. 2011;6(1):e14535. Published 2011 Jan 14.
21. FM Buonaguro; ML Tornesello; L Buonaguro; RA Satriano; E Ruocco; G Castello; V Ruocco (2003). Kaposi's sarcoma: aetiopathogenesis, histology and clinical features. , 17(2), 138–154.
22. Koop, H. O., Holodniy, M., & List, A. F. (1987). Fulminant Kaposi's sarcoma complicating long-term corticosteroid therapy. The American Journal of Medicine, 83(4), 787–789.
23. Hertzler G, Gordon SM, Piratzky J, Henderson JM, Gal AA. Case report: fulminant Kaposi's sarcoma after orthotopic liver transplantation. Am J Med Sci. 1995;309(5):278-281.
24. Etemad, Shervin A, and Anna K Dewan. "Kaposi Sarcoma Updates." Dermatologic clinics vol. 37,4 (2019): 505-517. doi:10.1016/j.det.2019.05.008
25. Lebbe C, Garbe C, Stratigos AJ, *et al*. Diagnosis and treatment of Kaposi's sarcoma: European consensus-based interdisciplinary guideline (EDF/EADO/EORTC). Eur J Cancer. 2019;114:117-127.
26. Higgins V, Sohaei D, Diamandis EP, Prassas I. COVID-19: from an acute to chronic disease? Potential long-term health consequences. Crit Rev Clin Lab Sci. 2021;58(5):297-310.
27. Melnikova VO, Dobroff AS, Zigler M, *et al*. CREB inhibits AP-2alpha expression to regulate the malignant phenotype of melanoma. PLoS One. 2010;5(8):e12452. Published 2010 Aug 27.
28. Daniel P, Filiz G, Brown DV, *et al*. Selective CREB-dependent cyclin expression mediated by the PI3K and MAPK pathways supports glioma cell proliferation. Oncogenesis. 2014;3(6):e108. Published 2014 Jun 30.
29. Zhou M, Liu X, Li Z, Huang Q, Li F, Li CY. Caspase-3 regulates the migration, invasion and metastasis of colon cancer cells. Int J Cancer. 2018;143(4):921-930.
30. Ebrahimi Sadrabadi A, Bereimipour A, Jalili A, Gholipurmalekabadi M, Farhadihosseinabadi B, Seifalian AM. The risk of pancreatic adenocarcinoma following SARS-CoV family infection. Sci Rep. 2021;11(1):12948. Published 2021 Jun 21.
31. Alpalhão M, Ferreira JA, Filipe P. Persistent SARS-CoV-2 infection and the risk for cancer. Med Hypotheses. 2020;143:109882.
32. Policard M, Jain S, Rego S, Dakshanamurthy S. Immune characterization and profiles of SARS-CoV-2 infected patients reveals potential host therapeutic targets and SARS-CoV-2 oncogenesis mechanism. Virus Res. 2021;301:198464.

33. Dursun R, Temiz SA. The clinics of HHV-6 infection in COVID-19 pandemic: Pityriasis rosea and Kawasaki disease. Dermatol Ther. 2020;33(4):e13730.
34. Saade A, Moratelli G, Azoulay E, Darmon M. Herpesvirus reactivation during severe COVID-19 and high rate of immune defect. Infect Dis Now. 2021;51(8):676-679.
35. Nasrullah A, Patel S, Ud Din MT, *et al*. A case of acquired immunodeficiency syndrome-related Kaposi sarcoma in a patient with COVID-19 - A brief review of HIV-COVID Co-infection and its Therapeutic challenges!. Respir Med Case Rep. 2021;34:101524.
36. Gardini G, Odolini S, Moioli G, *et al*. Disseminated Kaposi sarcoma following COVID-19 in a 61-year-old Albanian immunocompetent man: a case report and review of the literature. Eur J Med Res. 2021;26(1):152. Published 2021 Dec 20.
37. Magri F, Giordano S, Latini A, Muscianese M. New-onset cutaneous kaposi's sarcoma following SARS-CoV-2 infection. J Cosmet Dermatol. 2021;20(12):3747-3750.
38. Aram K, Patil A, Goldust M, Rajabi F. COVID-19 and exacerbation of dermatological diseases: A review of the available literature. Dermatol Ther. 2021;34(6):e15113.
39. Temiz SA, Kutlu Ö. The development of dermatologic diseases in patients recovered from COVID-19. Dermatol Ther. 2021;34(2):e14791.
40. Leoni E, Cerati M, Finzi G, Lombardo M, Sessa F. COVID-19 and HHV8 first spotted together: an affair under electron microscopy. J Eur Acad Dermatol Venereol. 2021;35(5):e311-e312.
41. Yanes, Ryan R *et al*. "Detection of SARS-CoV-2 and HHV-8 from a large pericardial effusion in an HIV-positive patient with COVID-19 and clinically diagnosed Kaposi sarcoma: a case report." Tropical medicine and health vol. 50,1 72. 24 Sep. 2022
42. J, Dai L, Barrett L, *et al*. SARS-CoV-2 proteins and anti-COVID-19 drugs induce lytic reactivation of an oncogenic virus. Commun Biol. 2021;4(1):682. Published 2021 Jun 3.
43. Cohen-Barak, Eran *et al*. "Kaposi's sarcoma in a patient with pemphigus vulgaris." International journal of dermatology vol. 55,1 (2016): 85-8.
44. Wang, Tao *et al*. "Identification of human herpesvirus-8 in Kaposi's sarcoma with bullous pemphigoid." Chinese medical journal vol. 127,4 (2014): 786-8.
45. Choi KH, Byun JH, Lee JY, Cho BK, Park HJ. Kaposi sarcoma after corticosteroid therapy for idiopathic thrombocytopenic purpura. Ann Dermatol. 2009;21(3):297-299.
46. Simeoni, Sara *et al*. "Dermatomyositis complicated with Kaposi sarcoma: a case report." Clinical rheumatology vol. 26,3 (2007): 440-2.
47. Zerbi S, Saruggia M, Brambilla L, Lodeville D, Buccianti G. Kaposi's sarcoma in a patient with focal glomerulosclerosis. J Nephrol. 2001;14(4):299-303.
48. L. Zhang, F. Zhu, L. Xie, C. Wang, J. Wang, R. Chen, P. Jia, H.Q. Guan, L. Peng, Y. Chen, P. Peng, P. Zhang, Q. Chu, Q. Shen, Y. Wang, S.Y. Xu, J.P. Zhao, M. Zhou, Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China, Annals of Oncology, vol. 31, Iss. 7, 2020, p. 894-901, ISSN 0923-7534.