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CLINICAL COMMENTARY

New-onset cutaneous kaposi's sarcoma following SARS-CoV-2 infection

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Abstract

Background: COVID-19 is associated with several cutaneous manifestations, including chilbain-like lesions, urticaria, erythema multiforme, and maculopapular lesions. Dermatoses may be directly linked to the viral infection or also represent a consequence of systemic therapies administrated for COVID-19. A potential role of SARS-CoV-2 in triggering the reactivation of other viruses, such as HHV-6, HHV-7 and Epstein-Barr virus has been hypothesized.

Objective: To better understand and hypothesize possible pathogenetic correlations of COVID-19 with other dermatological conditions.

Methods: We report the case of an 83-year-old woman hospitalized in a nursing home for several years. On November 2020, the patient had been diagnosed with SARS-CoV-2 infection, with repeated positive swabs until January 2021. After a month, new-onset asymptomatic cutaneous purplish macular lesions and violaceous patches occurred bilaterally on the feet.

Results: An incisional cutaneous biopsy and the histological examination of the plantar lesion revealed the diagnosis of Kaposi Sarcoma.

Conclusion: We report a unique case of new-onset bilateral Kaposi's sarcoma following COVID-19, speculating on a possible role of SARS-CoV-2 in the reactivation of human herpes virus-8 (HHV-8) infection.

KEYWORDS
COVID-19, kaposi sarcoma, SARS-CoV-2

1 | INTRODUCTION

Coronavirus disease (COVID-19) has spread across the globe from December 2019 causing the current pandemic. Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), an RNA virus of the beta-coronavirus family is the responsible of the disease.[1] COVID-19 may range from mild symptoms to pneumonia with acute respiratory distress symptoms (ARDS) and multiorgan dysfunction.[2] Besides COVID-19-related respiratory symptoms, several cutaneous manifestations have also been largely documented, including chilblain-like lesions, urticaria, erythema multiforme, and maculopapular lesions.[1] Dermatoses may be directly linked to the viral infection or also represent a consequence (such as urticarial eruptions) of systemic therapies administrated for COVID-19.

Interestingly, a possible role of SARS-CoV-2 in triggering the reactivation of other viruses, such as HHV-6, has been hypothesized.[3]

Here, we report a unique case of bilateral Kaposi's sarcoma (KS) of the plantar region in an 83-year-old woman which occurred following SARS-CoV-2 infection, speculating on a possible role of SARS-CoV-2 in the reactivation of human herpes virus-8 (HHV-8) infection.

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1.1 | Case description

This case regards an 83-year-old Caucasian female patient from Southern Italy, hospitalized in a nursing home for several years, and affected by arterial hypertension, cognitive impairment, and bipolar disorder. Her long-term therapy included memantine, clozapine, nimodipine, amlodipine, clopidogrel, cholecalciferol, levothyroxine, atenolol, and pantoprazole. On November 26, 2020, the patient had been diagnosed with SARS-CoV-2 infection, following positive naso-oropharyngeal swab test. The patient had fever (37.5–38.5°) and weakness and after few days interstitial pneumonia occurred. Oxygen saturation ranged between 91% and 96% and diffuse "harsh" breath sounds with no abnormal lung sounds were present. Oxygen therapy was prescribed for one month (maximum FiO2 administrated 40%). In addition, the patient was treated with subcutaneous heparin injections, systemic antibiotics, and systemic steroids. The steroid treatment was initiated with dexamethasone 8 mg/day. After 10 days, the dose was gradually reduced, but the inflammatory response started again, so the dose was increased again to 8 mg/day. After one week, we tried again to slowly reduce the dose halving the dose of dexamethasone and then switching to the oral assumption of methylprednisolone 16 mg. The latter was followed by methylprednisolone 4 mg, and then, we progressively reduced the dose, until the interruption after 6 weeks. Totally, the patient assumed systemic steroids for 8 weeks.

On January 5, 2021, the naso-oropharyngeal swab test was repeated with negative result.

At the end of January 2021, new-onset asymptomatic cutaneous lesions occurred bilaterally on the feet and a dermatology consultation was scheduled.

As reported by the patient's family physician, roundish red spots firstly appeared on the plant and ventral part of the fingers. A large violaceous patch appeared after a few days.

On physical examination, multiple purplish tender macular lesions were present bilaterally on the plantar regions and a single purplish patch with irregular borders was located in the central part of the plantar areas, with few nodules at the periphery of the patch. Multiple isolated red spots were diffusely present in the whole plantar region, including the posterior region of fingers (Figure 1).

Dermoscopy showed a reddish-violaceous diffuse homogenous pattern (Figure 2). An incisional biopsy was performed on a purplish single nodule of the left plantar region, and the histological examination revealed dermal proliferation of spindled cells and vascular clefts filled with erythrocytes confirming the diagnosis of Kaposi Sarcoma. Chest X-ray did not show any obvious abnormalities; HIV test and HCV-RNA had a negative result, while HHV-8 antibodies were positive. Esophagogastroduodenoscopy and colonoscopy have been scheduled but the patient's family refused the examinations. The patient is currently on clinical follow-up.

2 | DISCUSSION

We report a unique case of KS following SARS-CoV-2 infection. Only one case of SARS-CoV-2-related KS has been reported so far in a

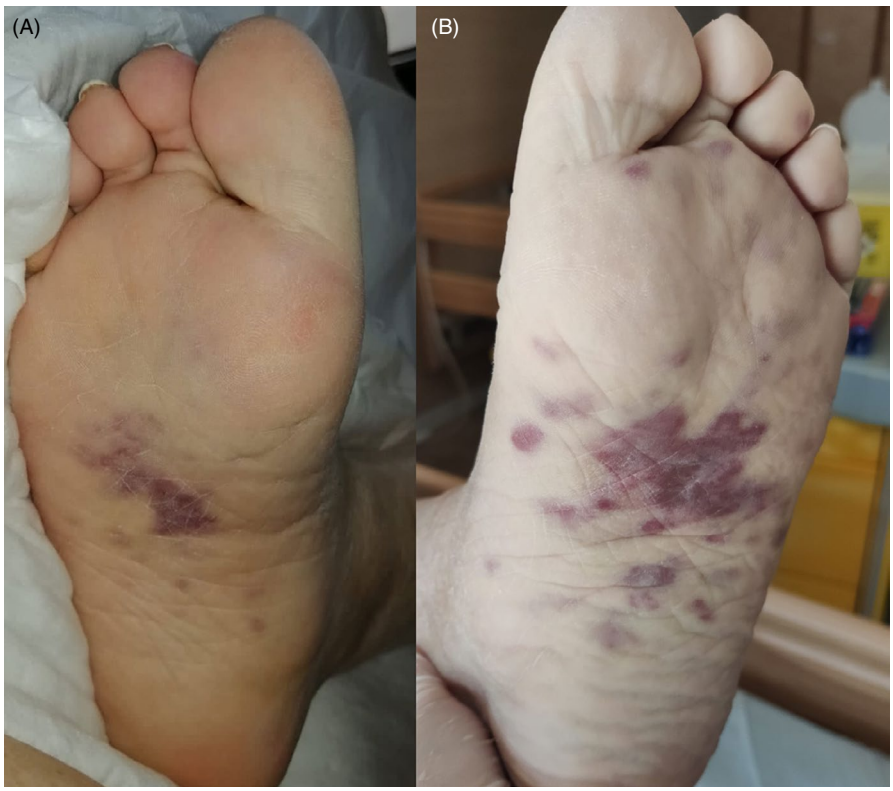

FIGURE 1 a-b: Multiple purplish tender macular lesions localized on the feet with a single purplish patch with irregular borders localized at the central part of the plantar areas, with few nodules at the periphery of the patch

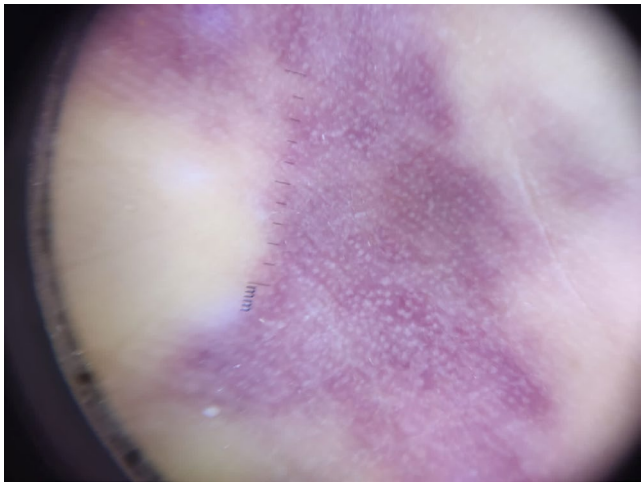

FIGURE 2 Dermoscopy showed a reddish-violaceous diffuse homogenous pattern. The patient has given consent for publication of patient information and images

patient with previous history of KS.[4] Thus, to the best of our knowledge, this is the first case of new-onset KS after COVID-19 in literature.

KS is divided in four variants: *classic*, *endemic* (in African young males), *iatrogenic* (in patients undergoing immunosuppressive therapies), and *epidemic* (in HIV patients).[5]

It affects the mucocutaneous regions and appears with painless purplish macules, nodules, and plaques, mainly localized at the lower limbs. It may also involve lymph nodes and viscera.

KS etiology is still not completely understood. KS is an angioproliferative tumor of endothelial origin strictly linked to HHV-8 infection, which has been documented in more than 95% KS lesions of all four variants.[6] HHV-8, also called KS-associated herpes virus (KHSV), is a member of the human γ-herpesvirus family and presents a life cycle divided in two phases, latent and lytic.[7]

After an acute infection, KHSV establishes the latent infection with low gene expression and no production of virions.[7] When latency is disrupted, KHSV is reactivated and switches to the lytic replication, increasing the gene expression, including genes with oncogenic and angiogenic properties.

Various triggers have been shown to switch KHSV from latency to lytic reactivation, such as immunosuppression, unbalanced pro-inflammatory cytokines, and viral co-infections.[7]

In particular, immunosuppression plays a main role: Studies have shown that decreased levels of T cells are associated with spontaneous lytic production.[7] Furthermore, low CD4 T cells levels in HIV-positive patients are directly associated with the development of KS.[7]

Also steroids or other immunosuppressive drugs have been largely associated with KS. Specifically, prednisolone and azathioprine are the most frequently drugs linked to the iatrogenic form of KS.[8] Studies suggest that steroids may induce KS by indirectly inhibiting the transforming growth factor beta (TGFb), which inhibits the growth of endothelial cells.[9] Furthermore, Hudnall et al.[10] have reported increased KHSV replication and activation of the lytic cycle after steroids administration in transfected cells. Thus, steroids may have two effects: the upregulation of endothelial cell proliferation and the activation of KHSV.[11]

Besides immunosuppression, concomitant viral co-infections, including HIV, herpes simplex virus type 1 and 2 (HSV-1, –2), HHV-6, and HHV-7, may be determinant causing the reactivation of KHSV by stimulating the release of inflammatory cytokines, such as oncostatin M (OSM), hepatocyte growth factor (HGF), interferon-gamma (IFN- γ), and toll-like receptors 7 and 8 (TLR7-8).[7]

Probably, in our case, several cofactors may have contributed to the onset of KS, such as the systemic administration of steroids for eight weeks, the general impairment, the old age of the patient. However, we can also speculate a possible role of SARS-CoV-2 co-infection.

As already described for other viral co-infections, SARS-CoV-2 may cause the switch of latent KHSV into the lytic replication by stimulating the release of pro-inflammatory cytokines.

In support of this, other authors have already hypothesized that SARS-CoV-2 may trigger the reactivation of other viruses, such as HHV-6, HHV-7, and Epstein-Barr virus (EBV), thus explaining the increased occurrence of these viral infections, especially Pytiriasis rosea, during the current COVID-19 pandemic.[6] Furthermore, Leoni et al. have recently described a case of KS after COVID-19 in a patient with previous history of KS.[4] The authors performed transmission electron microscope (TEM) analysis in a patient's specimen, showing the co-presence of SARS-CoV-2 and KHSV, for which they speculated mechanisms of co-infection of these pathogens and also suggested a possible key role of IL-6.[4]

Interestingly, Chen et al. have recently reported that SARS-CoV-2-encoded proteins and anti-COVID-19 drugs are able to induce lytic reactivation of KSHV, suggesting that in KSHV+individuals, especially in endemic areas, the exposure to coronavirus may increase the risk to develop virus-related tumors.[12]

Besides the pathogenic implications, another interesting aspect of our case is its possible differential diagnoses. Generally, the purplish-violaceous lesions of KS may be confused with other conditions, such as ecchymosis, bacillary angiomatosis, hemosiderotic hemangioma, pyogenic granuloma, and pseudomyogenic hemangioendothelioma.[13,14] Furthermore, KS may mimic chilblains,[15] and chilblain-like lesions have been largely described as a COVID-19 skin manifestation. In our case, the initial onset of roundish violaceous spots on the feet and especially on the posterior region of the fingers could be easily confused with this frequently reported sign of COVID-19. Thus, physicians working in COVID-19 hospital should be aware of this possible, even if uncommon, differential diagnosis of chilblain-like lesions.

In conclusion, we reported this case to add new knowledge concerning possible cutaneous conditions associated with SARS-CoV-2 and COVID-19 therapies, suggesting possible pathogenic explanations of the onset of KS in our case and highlighting some challenging differential diagnoses.

CONFLICT OF INTERESTS

None.

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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