households of patients who experienced relapse, suggesting that they were exposed to the same trigger event.

We observed a relatively high frequency of relapses in our chilblain-like cohort. These relapses were contemporary with the second wave of the COVID-19 pandemic in our region. Recent data suggested that recurrent pernio could be linked to exposure to cold temperature.[6] In our area, the mean minimum and maximum temperatures ranged from 12·7 °C and 19·6 °C in October 2020 to 5·3 °C and 14·6 °C in January 2021. We cannot exclude that those relapses were caused by the return of the cold season triggering relapse on a previously altered microcirculation. Recurrent pernio occurs after cold exposure in genetic interferonopathies, supporting a seasonal explanation for the relapses. However, one-third of the patients who had relapses were exposed to possible or proven cases of COVID-19 within the household, and infections in the household were observed in 75% of cases within 2 weeks of the relapse of chilblain-like lesions. Conversely, COVID-19 infection was not reported in any patients or their households in the no-relapse group. Only one patient with relapse had a positive PCR test. Despite proven circulation of the virus in the household, virological confirmation of infection is lacking in most patients.

Chilblain-like lesions associated with the COVID-19 pandemic have been suggested as interferon type I-related skin manifestations due to an efficient antiviral response in those patients.[4,7] Efficient antiviral immune response has been proposed to explain the absence of virological confirmation in children exposed to COVID-19 within households.[8] This probably explains the difficulties in proving a causal link based on a positive RT-PCR and/or serology between chilblain-like lesions and COVID-19.

Taken together, our results suggest an eventual high risk of relapses in patients who have had a previous episode of chilblains in the context of COVID-19 infection. Our data suggest that re-exposure to SARS-CoV-2 infection might trigger a relapse in chilblain-like lesions, although we cannot exclude that an initial insult from SARS-CoV-2, followed by subsequent cold exposure, could trigger these relapses in some cases.

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Funding sources: Centre Hospitalier Universitaire de Nice, France.

Conflicts of interest: the authors declare they have no conflicts of interest.

Kawasaki-like multisystem inflammatory syndrome associated with COVID-19 in an adult: a case report

DOI: 10.1111/bjd.20574

Dear Editor, As the COVID-19 pandemic continues to surge, the varied spectrum of clinical presentations keeps growing. The US Centers for Disease Control and Prevention (CDC) has recently described COVID-19-associated multisystem inflammatory syndrome in adults (MIS-A), which presents as an amalgam of Kawasaki disease (KD) and toxic shock syndrome (TSS).[1,2] We report a 22-year-old Indian man with 5 days of fever, headache, myalgia and skin rash, and a one day history of lower-extremity and upper-abdominal pain, and vomiting.

COVID-19 reverse-transcriptase polymerase chain reaction (RT-PCR) at admission was negative. He was febrile (104·6 °F), tachypnoeic (36 breaths per min) and tachycardic (122 beats per min), but was maintaining blood pressure (104/62 mmHg) and SpO_2 (98% room air). Dermatological examination revealed bilateral nonexudative conjunctival injection; hyperpigmented fissured lips; generalized erythema with multiple well-defined, discrete-to-coalescing, hyperpigmented macules involving the face, trunk and all extremities; and oedema of both hands and feet (Figure 1a–c). These findings were suggestive of KD as per the American Heart Association (AHA) criteria, although cervical lymphadenopathy was absent.

Investigations (normal levels in brackets) revealed haemoglobin 9·2 g dL^{-1}; total leucocyte count 11 820 cells μL^{-1} with 81% neutrophils, 10% lymphocytes and 5% eosinophils; bilirubin 1·2 mg dL^{-1}; aspartate transaminase 162 IU L^{-1} (5–40);

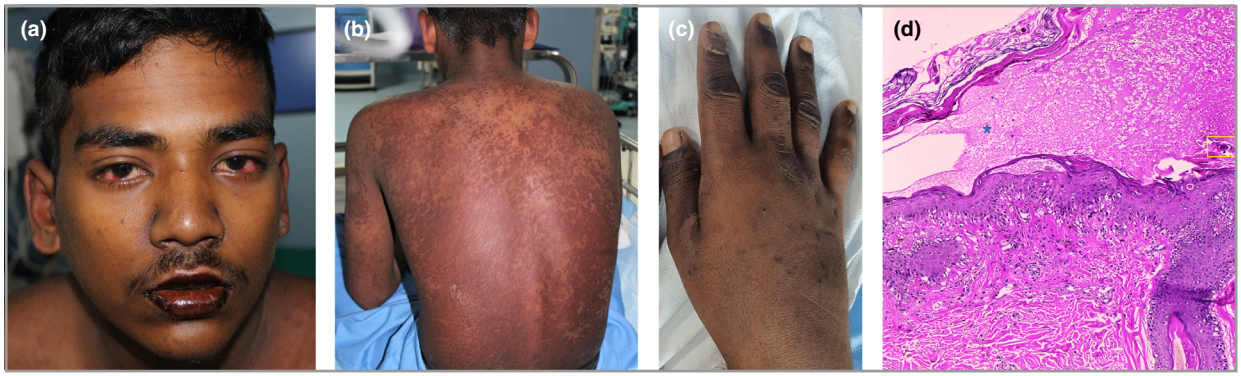

Figure 1 (a) Bilateral nonexudative conjunctival injection and swollen hyperpigmented chapped and fissured lips. (b) Generalized diffuse erythema and multiple well-defined, discrete-to-coalescing, hyperpigmented macules involving the trunk. Nikolsky's sign was negative. (c) Oedema of the hand is appreciable. (d) Skin biopsy from a truncal lesion shows a subcorneal split with red blood cells and fibrin within it (blue star). Stratum corneum shows parakeratosis and few haemosiderin-laden macrophages (yellow box). Focal apoptotic keratinocytes, spongiosis with irregular acanthosis and basal cell vacuolation are seen, with the upper dermis showing perivascular oedema and a mixed inflammatory infiltrate. Haematoxylin and eosin, original magnification × 200.

alanine aminotransferase 1171 IU L^{-1} (16–63); protein 6·2 g dL^{-1} (5·7–8·2); albumin 1·7 g dL^{-1} (4·0–4·7); triglycerides 253 mg dL^{-1} (< 150); erythrocyte sedimentation rate 92 mm h^{-1}; C-reactive protein 24 mg dL^{-1}; lactate dehydrogenase 505 U L^{-1} (81–234); creatine phosphokinase 341 U L^{-1} (26–192); ferritin 7410 ng mL^{-1} (23–336); procalcitonin 3·48 ng mL^{-1} (0–0·5); troponin I 81 ng L^{-1} (0–50); D-dimer 400 ng dL^{-1} (0–200); fibrinogen 398 mg dL^{-1} (200–400); interleukin-6 54·9 pg mL^{-1} (< 6·4) and sinus tachycardia on electrocardiogram. Chest X-ray and computed tomography (CT) showed bilateral pleural effusion. Transthoracic echocardiography (TTE), with 65% left ventricular ejection fraction, and CT coronary angiography did not reveal any abnormality.

Differentials of KD, TSS and haemophagocytic lymphocytosis (HLH) were considered. The skin biopsy findings are shown in Figure 1(d). Absence of hypotension and negative blood cultures ruled out TSS. Bone marrow showed no haemophagocytosis and the HLH-2004 criteria were not met.[3] Repeat COVID-19 RT-PCR was negative, while anti-SARS-CoV-2 antibodies were raised to 18 AU mL^{-1}, confirming prior COVID-19 infection. With positive anti-SARS-CoV-2 antibody, characteristic skin rash, and systemic features and investigations, the patient was diagnosed with COVID-19-associated Kawasaki-like MIS-A (K-MIS-A). He was empirically managed with low-molecular-weight heparin and antibiotics until initial negative blood cultures were available, and was discharged after 14 days with desquamation over the palms, soles and body, and stabilization of vital parameters and systemic symptoms. Repeat TTE and CT coronary angiography at 2 and 4 months did not show any cardiac abnormality. We plan to follow up the patient for 1 year to look for any sequelae.

Several features of our patient raised concern for K-MIS-A. He fulfilled the AHA criteria for KD and the CDC working MIS-A case definition.[1] MIS-A might be a phenotype with a combination of KD, TSS and macrophage activation syndrome, which are syndromes associated with hyperinflammation and dysregulated immune response in reaction to infectious triggers or current infection.[1,2] A lot of evidence has reported differences in clinical presentation, investigations and immunological responses in KD and MIS in children (MIS-C), concluding that the pathophysiology may be different. As such, MIS-C and MIS-A may be new and multifaceted entities distinct from KD.[4]

To date, five cases have shown features of K-MIS-A similar to our patient's.[1,2] People of all ages can develop MIS either with concurrent SARS-CoV-2 infection or as a postinfectious phenomenon, as 30% of cases of MIS-A had negative PCR but positive COVID-19 antibodies.[1] It took 2–5 weeks to develop MIS-A following onset of COVID-19 symptoms.[1] Hence, it becomes pertinent to examine COVID-19 antibodies along with RT-PCR for recognition of MIS-A.

The most common liver abnormality is aminotransferase elevation owing to direct, ischaemic or drug-induced liver injury leading to cytolysis.[5] Similarly, troponin elevation is attributed to mechanisms like cytokine release causing both direct and indirect myocardial injury through suppression of angiotensin-converting enzyme 2 (ACE2) and plaque instability in coronary vessels, SARS-CoV-2 targeting myocardial ACE2 receptors, and oxidative-stress-mediated endothelial dysfunction.[6] Hence, on a background of multifactorial pathogenesis, the most plausible explanation would be a virus-mediated immunogenic response triggering multisystem inflammation. Our patient probably had systemic capillary leak syndrome secondary to COVID-19, evident from hypoalbuminaemia and pleural effusion but without haemoconcentration or hypotension.[7] The patient initially had eosinophilia, which had settled by the third day of admission. This contrasts with eosinopenia, seen in severe COVID-19. Eosinophils have been associated with severe coronary vasculitis and aneurysms in KD.[8] Hence, the presence of eosinophilia may hint towards KD or K-MIS-A.[5,8]

Potential therapies used in MIS-A include intravenous immunoglobulin (IVIg), aspirin, anticoagulation, corticosteroids and tocilizumab.[1] With our evolving understanding of K-MIS-A, treatment protocols are yet to be standardized. Although we gave only anticoagulants to our patient, he recovered completely without any cardiac sequelae, as seen at follow-up. The CDC's detailed data on 27 cases of MIS-A included two cases with deranged inflammatory markers, ECG and TTE changes, which recovered on only anticoagulants without IVIg or steroids.[1] Hence, there might be a subset of patients with K-MIS-A who may recover spontaneously without conventional therapies. The focus of our case is to reiterate the possibility of COVID-19-associated K-MIS-A and timely diagnosis through early identification of dermatological manifestations and antibody testing, even when COVID-19 RT-PCR is negative. Further information on the investigations is available on direct request.

Acknowledgments: We are thankful to the Department of Pathology and Radiology, Command Hospital Air Force Bangalore, India for their necessary support.

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Funding sources: none.

Conflicts of interest: the authors declare they have no conflicts of interest.

Multifocal extracardiac rhabdomyomas: extending the phenotype of Birt–Hogg–Dubé syndrome

DOI: 10.1111/bjd.20521

Dear Editor, Birt–Hogg–Dubé (BHD) syndrome is characterized by a triad of benign skin tumours, pulmonary cysts with an attendant risk of pneumothorax and renal cancer. BHD is caused by heterozygous pathogenic variants in *folliculin* (*FLCN*), a tumour suppressor gene. Single cardiac and extracardiac rhabdomyomas have been infrequently reported[1] in patients with BHD, but not conclusively linked as part of the phenotype as these may have been coincidental events. Here we report a case of a patient with BHD with multifocal extracardiac rhabdomyomas, adding evidence to support rhabdomyomas as part of the BHD phenotype.

A 63-year-old man presented complaining of fullness in the submandibular region. He had multiple facial fibrofolliculomas and trichodiscomas (Figure 1a), for which he previously received ablative laser therapy. He was known to carry a familial heterozygous germline pathogenic variant in *FLCN* [NM_144997.5: c.469_471delTTC (p.Phe157del)] and had two brothers who were also carriers of the pathogenic variant. This variant segregated with the BHD phenotype in this family and has been reported in several prior BHD syndrome pedigrees.[1] One affected brother had a history of unilateral human papillomavirus-positive tonsillar squamous cell carcinoma, which had metastasized to the lymph nodes. Ultrasound and computed tomography studies of the head and neck in the proband demonstrated three homogeneous soft-tissue masses within the left submandibular and bilateral sublingual spaces (Figure 1b). A percutaneous ultrasound-guided core biopsy was obtained from the left submandibular tumour. Histological examination revealed large eosinophilic cells with occasional cross-striations, interspersed with pale areas. Immunohistochemistry demonstrated strong positivity for desmin in keeping with rhabdomyoma (Figure 1c). Rhabdomyoma DNA analysis demonstrated loss of heterozygosity (LOH) at the site of the patient's *FLCN* pathogenic variant, compared with control tissue (Figure 1d). Subsequent imaging has shown these tumours to have remained static over a 4-year period.

Extracardiac rhabdomyomas are categorized as adult, fetal and genital types.[2] Adult-type extracardiac rhabdomyomas have a predominance in men (average age of presentation 65 years) with the head and neck being the main site.[3] Patients may present with dysphagia and hoarseness, and other symptoms may include pain and new-onset snoring. Multifocal extracardiac rhabdomyomas are rare, with 33 cases ever reported, predominantly in male patients over the age of 50 years.[3] Such cases are suggestive of a genetic predisposition; however, unlike cardiac rhabdomyomas