developed relapsing CLL with or without other persistent cutaneous manifestations.

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The study was performed in accordance with the principles outlined in the Declaration of Helsinki and all patients have given their informed consent to participate in this study.

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Dapsone-induced methaemoglobinaemia in leprosy: a close mimic of 'happy hypoxia' in the COVID-19 pandemic

Dear Editor,

A 24-year-old man, native of Bihar, India presented with a numb, ring like reddish patch over the left foot since 14 months (Fig. 1).

Dermatological examination revealed a solitary, well-defined, hypotrichic, hypohidrotic, annular plaque, 7 cm in diameter over the dorsum of the left foot which was hypoaesthetic to pain, touch and temperature. No satellite lesions or nerve to patch was present. Left posterior tibial nerve and superficial peroneal nerve were thickened and non-tender.

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Patient was diagnosed as a case of Hansen's Disease (Borderline Tuberculoid) and was started on Multidrug Therapy (MDT) consisting of Rifampicin, Dapsone and Clofazimine since 07 February 2021. He presented for review on 20 February 2021 when he was incidentally detected to have oxygen saturation 88–90% on room air and was admitted as coronavirus disease 2019 (COVID-19) suspect. Patient had no respiratory symptoms, history of contact with COVID-19 patient or recent travel. Nasopharyngeal swab RTPCR for COVID-19 was negative, and chest X-ray revealed no abnormality. Arterial blood gas measurement was within normal limits and complete haemogram, biochemistry, urinalysis and ECG were normal.

Patient was reassessed and found to have a mild cyanotic hue over his fingers (Fig. 2). With suspicion of methaemoglobinaemia, blood was drawn for visual inspection, which revealed a chocolate brown colour. Methaemoglobin estimation in blood was done by spectrophotometry which revealed it to be 33.3% (Biological reference intervals: 0–2.0%). Based on temporal history of Dapsone intake, patient was suspected to have dapsone-induced methaemoglobinaemia. Dapsone was omitted from the MDT regimen. Patient was closely monitored for progression of symptoms, and oxygen saturation was monitored with pulse oximetry. Within 72 h, cyanosis resolved and oxygen saturation levels returned to normal.

Pulse oximetry has become an important part of clinical assessment of patients in the COVID-19 pandemic, and its use has greatly expanded. A pulse oximeter emits light of two different wavelengths, 650 and 805 nm and estimates the proportion of light absorbed and thus the proportion of oxyhaemoglobin; however, it cannot detect other forms of haemoglobin such as methaemoglobin. When other forms of haemoglobin are present in blood, a difference between the oxygen saturation estimated by pulse oximetry and arterial partial pressure of oxygen by blood gas analysis, or so-called 'saturation gap' is seen. This has

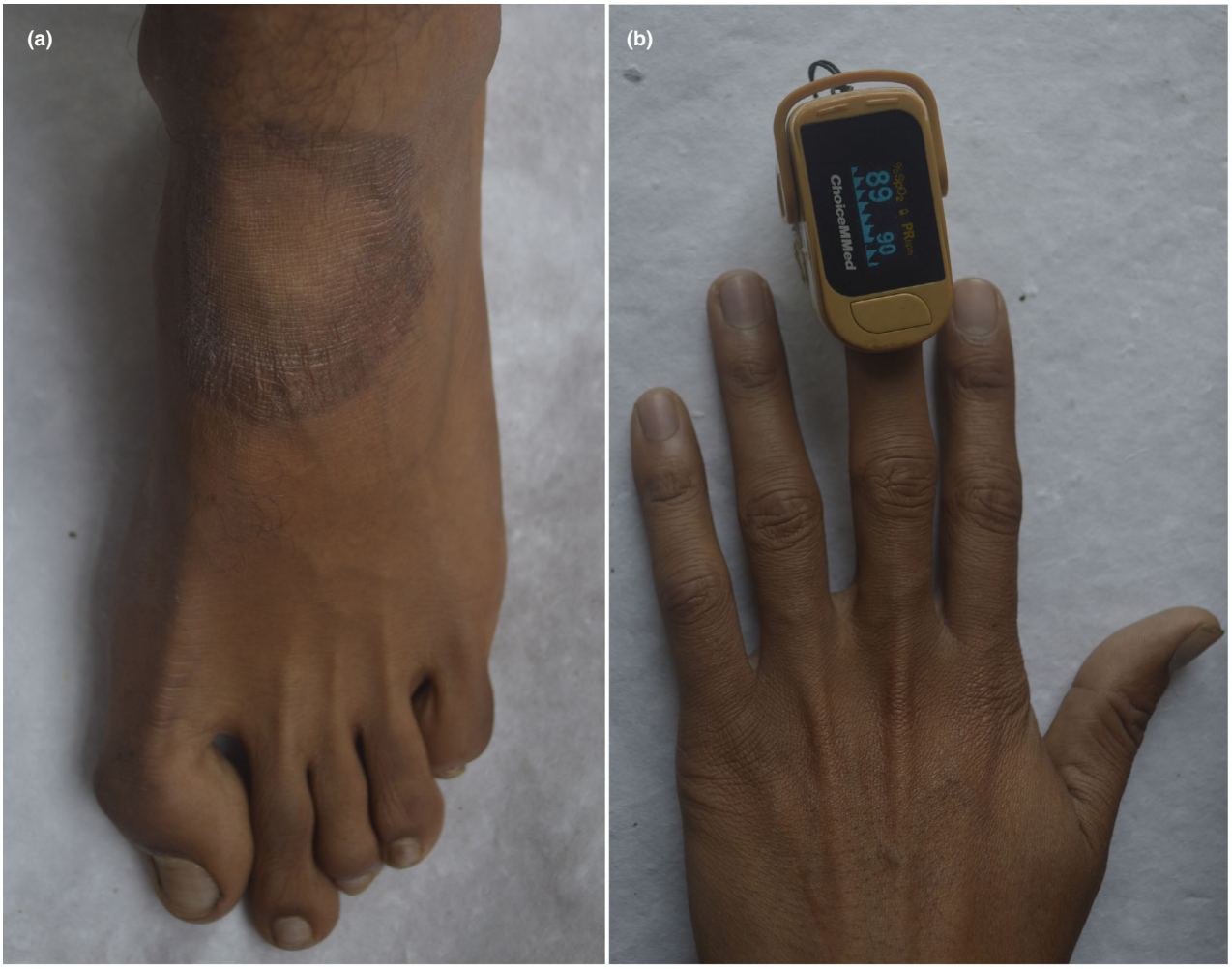

Figure 1 (a) Annular plaque on left foot. (b) Pulse oximeter showing abnormal reading.

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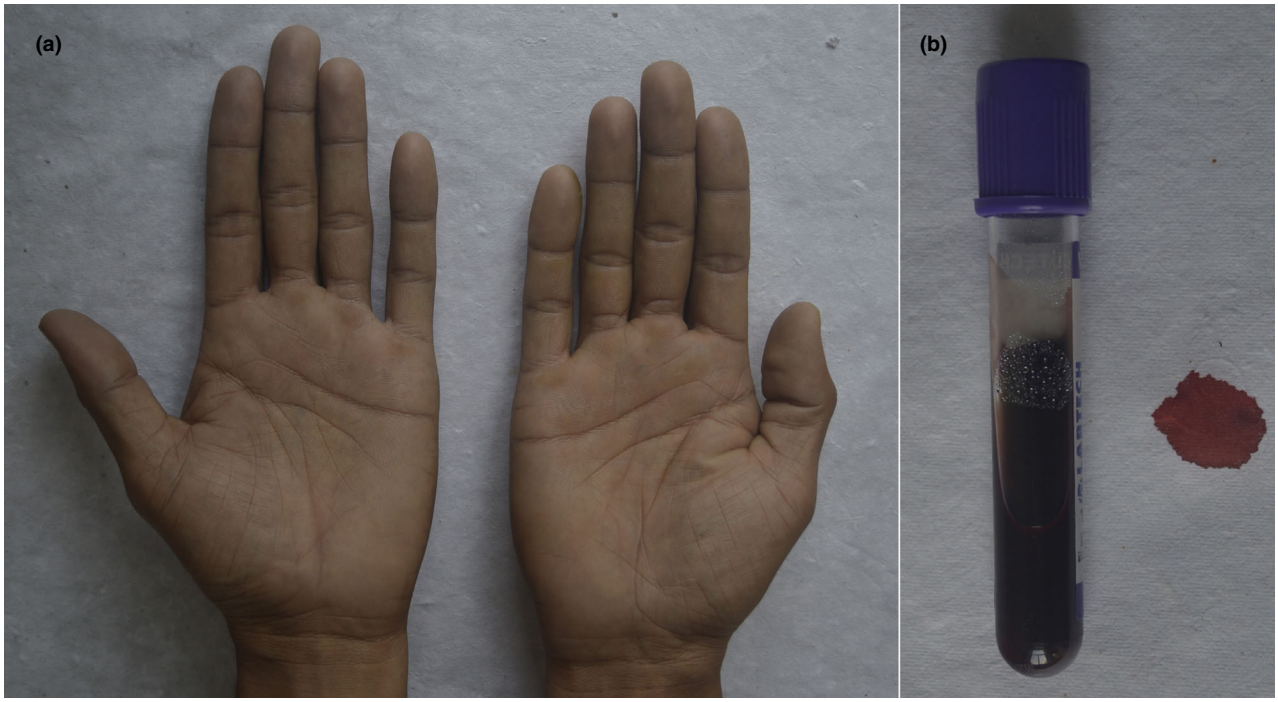

Figure 2 (a) Cyanotic hue visible over fingers. (b) Chocolate-coloured venous blood and the same when blotted on filter paper.

increased the detection of methaemoglobinaemia, which is otherwise a rare disease.[1]

Methaemoglobin is a form of haemoglobin where iron is present in the ferric state instead of the ferrous state, thus making it incapable of binding and transporting oxygen. The causes of methaemoglobinaemia can be hereditary or acquired, which includes drugs and toxins like Dapsone which are strong oxidizing agents. When levels of methaemoglobin exceed 1–2% of the total haemoglobin, methaemoglobinaemia is said to be present. Levels of <25% are generally asymptomatic. Clinical manifestations can range from cyanosis, fatigue, headache to seizures, arrhythmias, coma and even death. Important clues to diagnosis are hypoxia which is refractory to oxygen supplementation and presence of chocolate-coloured blood.[2,3]

Treatment ranges from simply stopping the offending drug in asymptomatic cases to methylene blue for symptomatic cases. Other options include high-dose ascorbic acid, exchange transfusion and hyperbaric oxygen therapy.[4] COVID-19 is also known to produce a similar condition known as 'happy hypoxia' in which patients have low oxygen saturation but are not manifesting clinical features of respiratory distress.[5] Arterial blood gas analysis helps in quickly differentiating between methaemoglobinaemia and 'happy hypoxia'. We should be watchful for both these conditions among dermatologic patients in the COVID-19 pandemic.

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Autoantibodies in Covid-19 – a model for viral induced autoimmunity

Dear Editor,

The novel Coronavirus SARS-CoV-2 is suspected of acting as a trigger for autoimmune diseases and the production of autoantibodies. Retinoic acid-inducible gene (RIG)-I-like receptors (RLR), including melanoma differentiation-associated protein 5 (MDA5) and RIG-I, recognize the double-strand (ds) virus RNA and induce the production of Type I interferon (Type I IFN) as well as pro-inflammatory cytokines like Interleukin (IL)-6[1] (Fig. 1). High IL-6 levels are associated with the induction of pro-inflammatory cytokines ("cytokine storm") and development of respiratory failure.[2] On the other hand, chronically high levels of Type I IFN are related to several autoimmune diseases such as systemic Lupus erythematodes (SLE), Sjögren Syndrom, systemic sclerosis, inflammatory myopathies and rheumatoid arthritis (RA). In terms of clinical presentation and biomarkers, many similarities can be found between Covid-19 and anti-MDA5 positive dermatomyositis.[2] Moreover, allelic variations within IFN-pathway-genes can be found in those autoimmune diseases.[3] The first cases of new autoimmune phenomena related to Covid-19 were found with some delay after the outbreak of the pandemic. With a new awareness for possible induction of autoimmune-mediated phenomena associated with SARS-CoV-2 infection, the topic gained attention. In recent years, the potential role of viruses in the pathogenesis of autoimmune diseases, e.g. Epstein-Barr-Virus, has been published.[4] There have also been reports of post-vaccination onset of autoimmune diseases, most recently following SARS-CoV2 vaccination.[5] Therefore, it stands to reason to consider SARS-CoV-2 as a trigger for autoimmune phenomena. We performed a meta-analysis of recently published articles on autoimmune phenomena associated with concomitant SARS-CoV-2 infection.[6–10] Table 1 shows reported autoantibodies, increased levels of IL-6 as well as frequently reported clinical symptoms.

Several authors reported an increased frequency of at least nine autoantibodies in patients with Covid-19, with Lupus Anticoagulant (LA) being the most common (75 out of 107 patients).

LA is associated with prolonged activated partial thromboplastin time (aPTT), arterial or venous thrombosis, and in consequence cardiovascular events. Besides LA, anticardiolipin- and anti-β_2-glycoprotein-I antibodies are numbered among the group of antiphospholipid antibodies and were found in three more cases. Congruent to these findings, Covid-19 patients often showed clinical signs of coagulopathies such as hypercoagulation and thromboembolic events including pulmonary embolism and stroke.[11,12] Microangiopathic changes were represented by chilblain-like skin lesions and eruptive cherry-angioma.[13] Kolivars *et al.* hypothesized that chilblain-like lesions and microangiopathic changes are due to immunologic reactions to the viral infection. In this case, the Type I IFN response most likely happens to be early and strong in young patients resulting in microangiopathy and chilblains, overall with a short and indolent course of the infection, whereas older patients react late and inadequately to Type I IFN, which results in hypercytokinemia, hypercoagulation, and thus with an increased morbidity and mortality.[14]

A potential reason for the significantly lower rate of six out of nine mentioned autoantibodies could be their delayed presence compared to LA and anticardiolipin IgA antibodies. Furthermore, severe and acute coagulopathies need rapid investigation, due to their ability to evoke an acute life-threatening situation. Therefore, most hospitals have implemented diagnostic algorithms. In contrast, autoantibody-screenings are not part of these routine work-ups. They are time consuming and are usually done posthoc. Additionally, in most cases patients' basal autoantibody levels are not available, making it difficult to give a clear statement regarding the coherence of autoimmune phenomena and antibodies with a SARS-CoV-2 infection. In our opinion, a correlation between a SARS-CoV-2 infection and autoimmune phenomena is likely, and we propose to consider autoantibody screenings more often in diagnostic procedures, keeping autoimmune phenomena as a differential diagnosis in mind. Further studies are needed for a more founded statement on/better understanding of the coherence of the appearance of autoantibodies following SARS-CoV-2 infection.

Conflicts of interest

JB declares to have no conflict of interest. SV declares to have no conflict of interest.

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