Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Cryoglobulinemic purpura and COVID-19 infection

Púrpura crioglobulinémica e infección por COVID-19

Dear Editor:

The patient is a 54-year-old woman, a former smoker, with a history of hypertension, asthma and osteoarthritis. She presented with a COVID-19 infection in early June 2021 with fever, dry cough and arthralgia. Following resolution of the symptoms at home, she visited the emergency department at the end of June for generalised arthralgia, skin purpura associated with burning pain in the lower limbs and buttocks, pitting oedema up to the thighs, low-grade fever, and hypertension. Additional tests showed microcytic anaemia with transfusion requirements, a nephritic syndrome with C3 complement consumption and elevated RF, with ANCA and other autoimmune tests with negative results. Serology was negative for syphilis, herpesvirus 2, HIV, HBV, HCV, and Epstein-Bar virus (EBV), with positive IgG for herpesvirus 1 and CMV. A transthoracic echocardiogram showed moderate pericardial effusion and septal hypertrophic cardiomyopathy, with no findings of infiltrative disease on cardiac MRI. A full-*body* CT ruled out neoplasm and ground glass interstitial infiltrates were detected with possible association to previous viral infection. The patient experienced clinical and laboratory improvement with symptomatic treatment, a tapering corticosteroid regimen and requested discharge due to transfer of home. In August she returned to the hospital with the same symptoms, was admitted and underwent a new study. Nephritic syndrome increased pericardial effusion to moderate-severe and resolution of pulmonary infiltrates on CT scan were observed. Additionally, IGRA and cryoglobulins were requested, which were positive; a skin biopsy reported leukocytoclastic vasculitis and a kidney biopsy detected cryoglobulinaemic membranoproliferative glomerulonephritis. The pericardial fluid study was compatible with exudate, without microbiological isolation, with negative TB PCR and absence of malignant cells. The study was completed with an electromyogram which revealed sensory-motor axonal polyneuropathy and a PET-CT scan which ruled out neoplastic disease or high-grade metabolic lesions. The definitive diagnosis was mixed cryoglobulinaemia with membranoproliferative glomerulonephritis, leukocytoclastic vasculitis and sensory-motor axonal polyneuropathy, with a recent history of COVID-19 infection. Severe pericardial effusion possibly related to previous COVID-19 infection. Latent tuberculosis. Treatment of cryoglobulinaemic syndrome will depend on the severity and, in any case, treatment of the underlying cause should be considered when it exists. Mild cases generally do not require immunosuppressive treatment and as the case becomes more severe, treatment will consist of corticosteroids and rituximab, considering corticosteroid pulses and plasmapheresis in case of a life-threatening situation or organ compromise.[1] The patient continued treatment with antihypertensives, analgesics, and anticonvulsants for neuropathic pain. As the origin of the pericardial effusion was uncertain, corticosteroids were not started and tuberculostatic agents were prescribed until the results of the mycobacterial fluid culture were negative. The patient showed clinical improvement, returned to normal laboratory parameters, and continued follow-up in outpatient visits with good clinical progression, stabilisation of renal function and adjuvant treatment for lower limb neuropathy.

Numerous cases of autoimmune disease have been described in association with COVID-19 infection, including several types of vasculitis, but no cases of cryoglobulinaemic vasculitis have been described so far, so this is an interesting case to add to the literature. Cryoglobulins are immunoglobulins (Ig) that precipitate at low temperatures, their presence in blood is called cryoglobulinemia and when they produce symptoms, the term cryoglobulinaemic syndrome is used.[1] This can be suspected in patients with arthralgia, skin purpura or ulcers, glomerulonephritis and peripheral neuropathy, such as our patient. Type I cryoglobulinaemia is composed of monoclonal Ig, it is associated with plasma cell dyscrasias and lymphoproliferative syndromes, while types II and III are grouped under the term mixed cryoglobulinaemia, are composed of polyclonal (III) or monoclonal and polyclonal (II) Ig and are associated with infections, systemic autoimmune diseases and lymphoproliferative syndromes. Regarding infectious processes, chronic HCV infection stands out, although cases with HBV have also been described and occasionally after infection with HIV, CMV, EBV and parvovirus B19.[2] Viral infections trigger an immune response in the host organism and can sometimes unbalance immune tolerance, giving rise to autoinflammatory and autoimmune disorders. In this sense, the COVID-19 virus has been related to diseases such as Guillain-Barré syndrome, autoimmune haemolytic anaemia and numerous vasculitides, such as paediatric inflammatory multisystem syndrome (a vasculitis with characteristics similar to Kawasaki disease) or chilblain.[3] Regarding the latter, cases of cryofibrinogenemia have been described in relation to the COVID-19 pandemic, as demonstrated by the Gómez-Fernández et al. series.[4] This vasculitis is characterised by the formation of erythematous plaques or purpuric macules located on the feet and toes. Cryofibrinogen precipitates are seen only in plasma, may contain Ig, but are composed primarily of fibrinogen, fibrin, fibronectin, or fibrin degradation products. One difference with cryoglobulins is that cryoglobulins are formed in serum and plasma. In relation to cryoglobulinemia, flares have been described after vaccination against COVID-19[5] in patients previously diagnosed with cryoglobulinemia, but there are no *de novo* cases described after infection. Our patient presented with a cryoglobulinaemic syndrome after infection, it is unclear whether the COVID 19 infection could be related to the imbalance in immune tolerance and cryoglobulin formation or act as a precipitant of a previously undiagnosed latent condition. What does seem clear is the link between COVID infection and cryoglobulinaemic syndrome.

Conflict of interests

The authors declare no conflict of interest.

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