



## SARS-CoV-2-associated cold agglutinin disease: a report of two cases

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Dear Editor,

Hematological manifestations reported in SARS-CoV-2 infection mainly include lymphocytopenia as a poor prognosis factor [1]. Thrombocytopenia can be associated with disseminated intravascular coagulation [2] or immune process [3]. Data regarding anemia are scarce and in line with a recent report on six patients with heterogeneous hemolytic anemia [4], we herein report on two patients with SARS-CoV-2-related cold agglutinin disease (CAD).

**Patient 1** A 43-year-old woman was admitted after a 10-day course of asthenia, fever, cough, diarrhea, and dyspnea. Her medical history comprised obesity and untreated multiple sclerosis. Nasopharyngeal Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) confirmed SARS-CoV-2 infection. Chest computed tomography showed a typical severe interstitial pneumonia. Hemoglobin was normal upon admission (13.1 g/dL). A treatment with oxygen support and antibiotics (ceftriaxone and azithromycin for 3 days then tazocillin for 3 days) was started, with a rapid improvement of respiratory parameters. At day 6, hemoglobin levels dropped to 6.1 g/dL, with hemolytic features (low haptoglobin, elevated bilirubin, and lactate dehydrogenase (LDH) levels). The direct antiglobulin test (4+) was positive with the presence of cold agglutinins (Fig. 1). Etiological workup for hemolysis was negative.

After poor initial transfusion efficiency, hemoglobin levels and hemolytic parameters improved.

**Patient 2** A 63-year-old man, with a medical history of hypertension, was admitted for severe acute respiratory syndrome in intensive care unit (ICU). In the last 2 weeks, he presented with fever, cough, and progressive worsening dyspnea. The nasopharyngeal RT-PCR confirmed a SARS-CoV-2 infection. The initial blood count showed a non-regenerative normocytic anemia (10.5 g/dL). As haptoglobin levels were unmeasurable (<0.08 g/L), contrasting with increased serum orosomucoid (2.35 g/L), a hemolytic process was suspected and the direct antiglobulin test was positive (C3 [4+] and IgG [2+]) with cold agglutinins (Fig. 1). At day 6 of hospitalization, hemoglobin level decreased to 8.2 g/dL. Etiological workup was negative. Hemoglobin improved within 9 days along with clinical improvement.

We here report two supplemental cases of SARS-CoV-2-associated autoimmune hemolytic anemia with cold agglutinins which seems to be a rare but nevertheless real complication of this condition. CAD was previously reported in association with viral infections and *Mycoplasma pneumoniae* infection. The pathophysiological mechanism might be related to an antigen cross-reaction with red blood cell secondary to

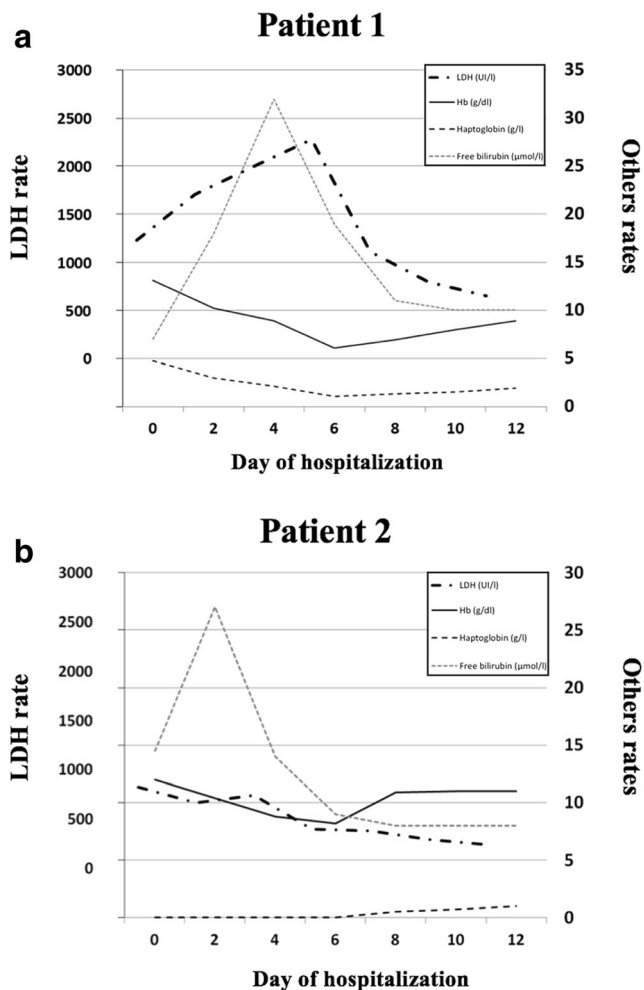
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**Fig. 1** Evolution of the biological parameters of cold agglutinin-associated hemolysis. **a** Evolution of the biological parameters of hemolysis in patient 1; **b** evolution of the biological parameters of hemolysis in patient 2

molecular mimicry, as with *Influenzae* disease [5]. A drug-induced CAD was considered uncommon [6].

We believe that a more extensive investigation of anemia in SARS-CoV2 patients, including the appraisal of hemolytic patterns might be useful for the detection of other cases of

CAD and appropriate management of anemia during SARS-CoV2-infection.

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**Author contribution** H.T., G.J., O.M., and S.D. designed the study, recruited patients, wrote, and reviewed, and R.M. and M.S. designed, reviewed, and approved the paper.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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