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COVID-19 infection associated with autoimmune hemolytic anemia

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Dear Editor,

A 62-year-old man with a medical past history of arterial hypertension and heavy smoking was ongoing radiochemotherapy for an oropharyngeal squamous cell carcinoma (cT3N0M0). Three days after the first cisplatin injection, the patient started a dry cough without fever. A nasopharyngeal swab was positive for Covid-19 (tested by PCR). A week later, he presented a marked asthenia and was referred to the emergency room. Physical examination showed fever and mild dyspnea, with a low oxygen saturation on room air. The patient was perfectly conscious, and there was no evidence of motor deficit. Chest X-ray showed bilateral lung infiltrates. The laboratory examination results were as follows: white blood cell count (WBC) 6620/ μ L, lymphocyte count 500/ μ L (NI, 800–5000), normal neutrophil count, platelet count 101,000/ μ L (NI, 150,000–450,000), hemoglobin 12 g/dL (NI, 13.3–16.7), CRP 45 mg/L (NI, < 5), normal serum creatinine, LDH 307 IU/L (NI, < 250), and bilirubin 0.7 mg/dL (NI, < 1.2).

Fourteen days after the first respiratory symptoms, he was transferred to the intensive care unit (ICU), and orotracheal intubation was required soon after admission. Anemia also deteriorated progressively with a rise of LDH level. On day 16, the patient developed acrocyanosis. Laboratory tests showed lymphocyte count 120/ μ L, normal neutrophil count, platelet count 145,000/ μ L, hemoglobin 6.9 g/dL, LDH 726 IU/L, reticulocyte count 40,000/ μ L (NI, 30,000–100,000) raising to 231,000/ μ L 10 days later, potassium 6.78 mmol/L (NI, 3.5–5), haptoglobin 0.13 g/L (NI, 0.3–2), CRP 335 mg/L, normal creatinine, and bilirubin 1.3 mg/dL. Blood smear showed numerous red blood cell agglutination, schizocytes < 1%. Direct Coombs test was

positive for C3b and negative for IgG. Cold agglutinins were positive (titer 1/16384) and anti-I (titer 1/1024). Antinuclear antibodies were positive (titer 1/160), ENA screening negative, and antiphospholipid negative. A multiplex PCR testing performed on tracheal aspiration was negative for *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, *Adenovirus*, and *Influenza*. Serology testing was negative for HBV, HCV, and HIV, while IgG antibodies were found for EBV and CMV and IgM and IgG antibodies for *Mycoplasma pneumoniae*. Leucocytes immunophenotyping performed on peripheral blood showed lymphopenia without evidence of clonality. There was an oligoclonal pattern of gammaglobulins at serum protein electrophoresis; light chains kappa/lambda ratio was normal. The patient received 8 units of red packet cells over 1 week. At 6-week follow-up, the patient is slowly recovering from respiratory failure.

While the main target of Covid-19 remains the lung, with respiratory failure and acute respiratory distress syndrome for the most severe cases, extra-pulmonary complications are now increasingly reported. Among autoimmune manifestations, autoimmune hemolytic anemia (AIHA) is an unusual finding. Autoimmune hemolytic anemia (with warm or cold antibodies) was recently described in 7 patients with Covid-19 disease [1, 2]. The delay between Covid-19 and hemolytic manifestations ranged from 4 to 13 days. Four patients had indolent B lymphoid malignancy either already known or discovered at the time of hemolytic episode. The chronological sequence in our case suggests that Covid-19 was the causal factor for AIHA. Temporal events and exclusion of other potential causes support this hypothesis. Indeed, our patient had a history of oropharyngeal carcinoma which is not usually considered as a triggering factor for autoimmune hemolytic anemia. The interpretation of *Mycoplasma pneumoniae* serology should also be extremely careful, as IgM antibodies do not mandatory indicate a recent infection [3]. In our case, PCR testing was negative on the sputum, and there was no significant increase in IgG antibody titer over time. Among other hematological complications of Covid-19 infection, autoimmune thrombocytopenia and antiphospholipid syndrome were also described, but not present in our observation [1, 4, 5].

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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.

Informed consent An informed consent was obtained from the relatives.

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