A misleading miscellanea: a COVID-19 patient with fever and cytopenia

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ABSTRACT

Complex clinical cases characterized by the coexistence of multiple pathologies and, consequently, multiple signs and symptoms shared by various pathological entities can hide pitfalls that may lead to incorrect diagnostic conclusions due to cognitive biases. Here, we present the case of a man who presents hyperpyrexia, progressive pancytopenia, and splenomegaly in the context of a SARS-CoV-2-related infection; the final diagnosis will be different from the initial diagnostic hypothesis.

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Introduction

Complex clinical cases with several illnesses coexisting and, thus, diverse signs and symptoms shared by different diseased entities can conceal cognitive biases that could lead to inaccurate diagnosis findings.

Case Report

We describe the case of an 86-year-old man, resident in the hilly area around Fidenza (Parma, Italy), hospitalized in the Internal Medicine Ward for malaise, progressive fatigue, and intermittent fever for approximately 5 days.

His medical history was noticeable for metabolic-related liver cirrhosis, with previous surgical liver resection for hepatocarcinoma, moderately compensated type 2 diabetes mellitus, and previous idiopathic pulmonary embolism treated with oral anticoagulant. He had no recent travel or sick contacts. Blood chemistry at admission revealed mild normocytic anemia (hemoglobin 10 g/dL), thrombocytopenia (130,000/mm^3), normal liver and kidney functions, polyclonal hypergammaglobulinemia, C-reactive protein elevation (120 mg/L) and minimal procalcitonin elevation (2 ng/mL).

The throat swab for SARS-Cov-2 was positive. The chest computed tomography (CT) scan showed right basal consolidation without signs of interstitial pneumonia.

On examination, he was alert, oriented, and collaborative; on auscultation, there were inspiratory crackles at the right lung base; the heart sounds were normal in the absence of murmurs; the abdomen was nontender; the spleen and liver were not palpable. He had no leg swelling, rash, or superficial lymphadenopathies.

The hospital course was initially characterized by a brief phase of hypoxemic normocapnic respiratory failure; since his medical history concerned us for a possible evolution in severe COVID-19 (advanced age, diabetes, liver cirrhosis), we administered Remdesivir obtaining rapid weaning from oxygen therapy.

Nonetheless, intermittent fever (thrice daily) persisted

with peak temperature at 40°C without response to paracetamol or non-steroidal anti-inflammatory drugs.

Suspecting a superimposed nosocomial bacterial infection, we started empirically broad-coverage antibiotic therapy without clinical response.

At the same time, the biochemical profile showed worsening pancytopenia, requiring transfusion of blood products, rising ferritin levels (2000) ng/mL, hypertriglyceridemia (280 mg/dL); the peripheral blood smear was negative for immature forms or schistocytes.

Abdominal ultrasound showed a new-onset moderate splenomegaly (area 75 cm^2) with regular echotexture. A repeated CT scan of the chest and abdomen showed no deep abscess.

In performing differential diagnosis, we considered multiple diagnostic possibilities: the normal coagulation tests and the absence of schistocytes in peripheral blood allowed us to exclude a form of thrombotic microangiopathy. The patient did not complain of any specific organ symptoms, and blood and urine culture tests were negative. He also did not take cytotoxic drugs, ruling out sepsis or toxic exposure. Since the patient was deteriorating, considering the constellations of signs and symptoms (pancytopenia, splenomegaly, and fever), we finally hypothesized both an atypical infectious disease or a systemic inflammatory syndrome post-COVID as the hemophagocytic lymphohistiocytosis (HLH), a multisystemic disease which has also been described in COVID patients.[1]

To confirm the diagnostic suspect, a bone marrow aspirate and biopsy were performed, and we started therapy with dexamethasone with partial defervescence.

Pending results for those examinations, *Leishmania Donovani* complex serology came back positive, as well as polymerase chain reaction, suggesting visceral leishmaniasis. Bone marrow aspirate showed macrophagic and plasma cellular hyperplasia with multiple amastigotes both outside and inside macrophages and neutrophils with signs of hemophagocytosis (Figure 1).

The steroid was stopped, and treatment with liposomal amphotericin B 3 mg/kg/day was started for 7 days, scheduled to repeat a dose on day 14 and day 21.

The patient had a prompt response to therapy and is currently doing physiotherapy exercises to resume walking. He denied owning dogs but reported that a neighbor owned a dog.

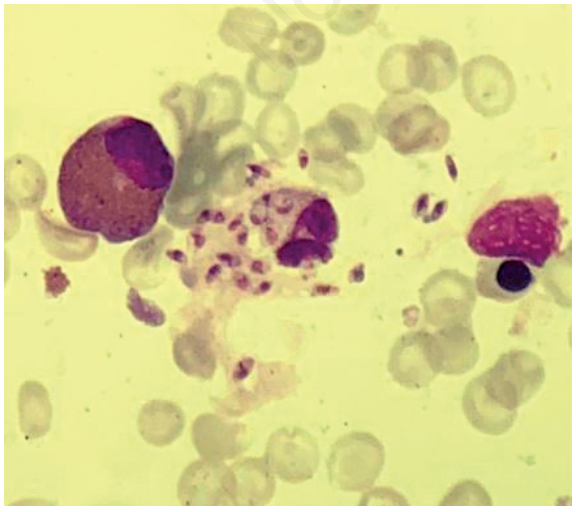

Figure 1. Bone marrow aspirate showed multiple Leishmania amastigotes.

Discussion and Conclusions

The present case was insidious because the SARS-Cov2-related infection with persistent fever, progressive pancytopenia, and the new-onset splenomegaly, along with hyperferritinemia and hypertriglyceridemia, led to a first diagnostic hypothesis of a systemic inflammatory disease such as hemophagocytic syndrome related to COVID infection. This dangerous miscellanea of signs and symptoms, shared by multiple diseases, was leading us astray, preventing us from giving the correct treatment.

The causes to be investigated in the differential diagnosis of pancytopenia are mainly divided into reduced bone marrow production (*e.g.*, aplastic anemia, systemic infection/inflammation, drugs related, due to neoplastic infiltration, due to radio-chemotherapy, and nutritional deficiencies) and increased peripheral consumption (*e.g.*, autoimmune diseases, hypersplenism, direct damage from drugs or infectious agents).

HLH can be primary [owing to genetic defects involving cytotoxic T cells and natural killer (NK) cells] or secondary (induced by infections and autoimmune or malignant disorders and usually associated with liver injury).[2]

The diagnosis of HLH requires the presence of five of the following eight criteria: i) fever (temperature ≥38.5°C); ii) splenomegaly; iii) peripheral blood cytopenia [with at least two of the following laboratory values: hemoglobin level <9 g per deciliter (<5.6 mmol per liter), a platelet count <100,000 per microliter, or an absolute neutrophil count <1000 per microliter]; iv) hypertriglyceridemia (fasting triglycerides level >265 mg per deciliter) or hypofibrinogenemia (fibrinogen level ≤150 mg per deciliter) or both; v) haemophagocytosis in the bone marrow, spleen, lymph nodes, or liver; vi) low or absent NK-cell activity; vii) a ferritin level ≥500 µg per liter; viii) an elevated level of soluble interleukin-2 receptor α.

A bone marrow biopsy/aspirate is part of the diagnostic work-up in unexplained pancytopenia since it can show signs of engulfment of hematopoietic cells by histiocytes in the bone marrow (*e.g.*, in HLH), immature forms (*e.g.*, hematological malignancy) or diminished blood cell precursors (*e.g.*, aplastic crisis).

Treatment of HLH involves therapeutic schemes based on systemic steroids and, in forms related to hematological diseases, etoposide.

The poor therapeutic response to the steroid led to diagnostic reconsideration which ultimately led to the correct diagnosis of visceral leishmaniasis, which can be associated with secondary hemophagocytosis unresponsive to steroids. Leishmaniasis is a parasitic disease caused by a protozoan, *Leishmania* spp. Leishmaniasis is a mammalian disease, and there are several widespread *Leishmania* species in the world; in Italy (as in other southern European countries) *Leishmania infantum* is widespread.

Zoonotic reservoir hosts include rodents (*L. major*, *L. amazonensis*, *L. mexicana*, *L. braziliensis*), marsupials (*L. amazonensis*, *L. mexicana*, *L. braziliensis*), edentates, and

monkeys (*L. braziliensis*), and canids (*L. infantum*).[3]

Parasites are transmitted through the bites of hematophagous females of some sandfly species of the genera *Phlebotomus* (Europe, Asia, and Africa) and *Lutzomyia* (Americas). The female sandfly ingests *Leishmania* amastigotes when she takes a blood meal and, if it is a permissive species, transmits the infective metacyclic stages at a subsequent blood meal

L. infantum can be transmitted from mother to child, female dog to puppy, and by shared syringes. The domestic dog is the only reservoir host of major veterinary importance.

In Italy, human and canine leishmaniasis has been present for a long time in the central-southern territories, but in recent decades, it has also spread to the northern-central regions, including Emilia-Romagna, where the mostly affected area is the hill and foothill area to the south of the *Via Emilia*.[4,5] Canine leishmaniasis always presents itself in a severe form.

Human leishmaniasis occurs in two forms: a milder form, cutaneous leishmaniasis, which heals in 100% of cases, sometimes even without treatment, or a more serious form, visceral leishmaniasis, which can lead to death if left untreated.

Visceral leishmaniasis does not cause lesions on the skin; it is a so-called "systemic" disease as the *Leishmania* parasite multiplies and spreads to all lymphatic organs (lymph nodes, spleen, liver, and bone marrow). The incubation period varies from about 10 days to several months.

The main signs and symptoms include: i) irregular fever (sometimes multiple fever spikes per day or periods without fever); ii) progressive enlargement of the lymph nodes, the liver, and the spleen; iii) weight loss and fatigue; iv) decrease in the number of white blood cells, erythrocytes, and platelets; v) increase in γ globulins.

Without treatment, most patients with the visceral disease will die and those with diffuse cutaneous and mucocutaneous involvement can suffer prolonged disease associated with secondary life-threatening infections. Treatment should be considered even for self-healing cutaneous leishmaniasis because it can lead to disfiguring scars.[6]

The first line treatment of visceral leishmaniasis in an immunocompetent patient is liposomal amphotericin B 3-5 mg/kg/die for 5-7 days and then repeated on days 14 and 21.[7]

To reduce bites of peridomestic vectors, insecticide-treated nets, and topically applied insecticides can be used. Dog collars impregnated with deltamethrin are used to control the infection of reservoir dogs.

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