Case report

Metastatic pulmonary dissemination as differential diagnosis of COVID-19 disease

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SUMMARY

A 13-year-old boy presented to hospital with 3-day self-limited fever, followed by dry cough, persistent asthenia and impaired general condition of 2 weeks' duration. Blood analyses showed a severe inflammatory status and chest X-ray images were consistent with bilateral COVID-19 pneumonia. He developed an acute respiratory failure that required paediatric intensive care admission and non-invasive ventilation. A targeted COVID-19 treatment was initiated with hydroxicloroquine, corticosteroids, enoxaparine and a single dose of tocilizumab. Repeated serological tests and real-time reverse transcription PCR for SARS-CoV-2 were negative. Other infectious pathogens were also ruled out. Thoracic high resolution CT showed an intense bilateral pulmonary dissemination with lytic vertebral bone lesions. After diagnostic investigations, Ewing's sarcoma with metastatic pulmonary dissemination was diagnosed. Nowadays, in the context of SARS-CoV-2 community pandemic, we cannot forget that COVID-19 clinical presentation is not specific and other entities can mimic its clinical features.

BACKGROUND

In the current context of COVID-19 pandemic, it is necessary to identify pathologies with a similar clinical–analytical presentation in order to define the differential diagnoses, especially in patients presenting at atypical ages or with repeatedly negative diagnostic tests. We report a case of metastatic pulmonary dissemination of Ewing's sarcoma with clinical presentation similar to COVID-19 disease.

CASE PRESENTATION

A 13-year-old boy presented with 3-day self-limited fever, followed by persistent asthenia and progressive cough for the previous 2 weeks. There was no history of contact with SARS-CoV-2 and all family members were asymptomatic. Blood analysis and a rapid antibody test using lateral-flow chromatographic immunoassay for SARS-CoV-2 were performed in a private laboratory showing a positive result for IgG and negative for IgM antibodies. He was then taken by his parents to a local community hospital for medical advice. On clinical assessment in emergency department, he showed a thoracic urticarial rash and reported lower back pain. At that time, he had started with fever again and was feeling unwell. Physical examination revealed a mildly impaired general condition without haemodynamic or respiratory instability. No hepatosplenomegaly, lymphadenopathy or meningism was observed. He denied dyspnoea, diarrhoea, dysgeusia or anosmia. Vital signs were within the normal range except for fever (38°C).

Chest radiography (figure 1) showed interstitial infiltrates in both lungs and laboratory examination revealed the following:

Leucocytes: 10×10^9/L; neutrophils:7.30×10^9/L; lymphocytes: 1.50×10^9/L; haemoglobin: 133 g/dL; platelets: 326×10^9/L;D-dimer: 5.161 µg/mL; international normalised ratio: 1.3; lactate dehydrogenase: 2.517 U/L;creatine kinase: 121 U/L; ferritin: 668 ng/mL; Creactive protein: 5.71 mg/dL; interleukin 6 (IL-6):70.9 pg/mL.

A second rapid antibody test (immunoassay) was performed, which was negative for SARS-CoV-2, and the study was completed with a SARS-CoV-2 reverse transcription PCR (RT-PCR) test in nasopharyngeal swab. Due to a high suspicion for COVID-19 disease with radiographical and analytical risk factors for severe presentation, the patient was transferred to our hospital, which is a tertiary level university hospital where a paediatric intensive care unit (PICU) facility is available. Initially, he was admitted to the paediatric general ward and treatment with hydroxychloroquine, enoxaparin at a prophylactic dose (1 mg/kg/day) and methylprednisolone (1.5 mg/kg/day) were started. New samples were collected for diagnostic study of SARS-CoV-2.

Four hours into his admission, the patient developed respiratory distress, tachypnea, tachycardia and progressive severe hypoxemia (arterial oxygen saturation (SaO_2)/fractional inspired oxygen (FiO_2) ratio: 150) and was taken to the PICU where non-invasive ventilation was initiated in continuous positive airway pressure mode. A single dose of tocilizumab (8 mg/kg) was then administered. Initial positive end expiratory pressure (PEEP) needed to be increased up to 9 cmH_2O to obtain a decrease in heart rate, breath rate and an enhanced SaO_2/FiO_2 ratio of 230 2 hours after the onset. In the following 48 hours, clinical status continued to improve, showing a better general condition without fever or asthenia and better respiratory parameters, what made it possible to decrease PEEP to 6 cmH_2O and fraction of inspired oxygen to 25%. In addition, increase in lymphocytes count and a decrease in the rest of the acute phase reactants were observed.

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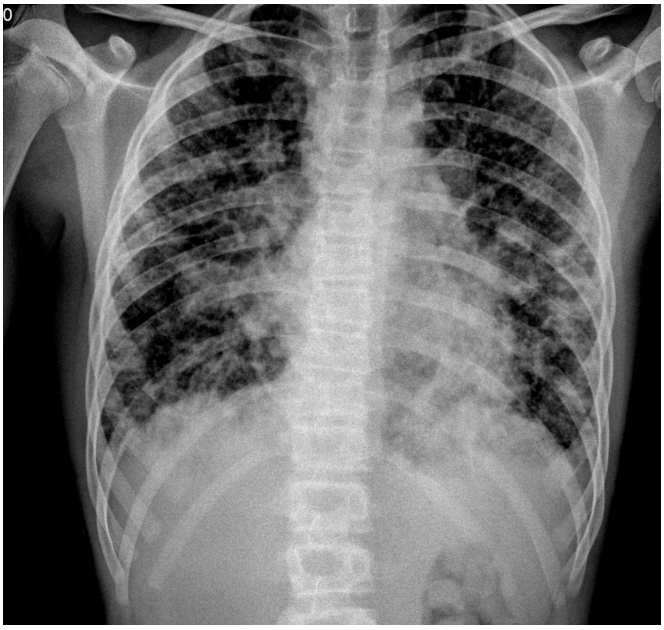

Figure 1 Chest X-ray. Day 1 X-ray showing diffuse peripheral patched lung consolidation, first considered compatible with a COVID-19 pulmonary disease pattern. No lytic images were seen on this projection.

INVESTIGATIONS

Rapid antibody blood test by immunoassay and RT-PCR nasopharyngeal swabs were performed at both hospitals, with negative results. After PICU admission and in view of these negative results, an ELISA test was performed, showing negative results too.

Diagnostic work-up was completed with serological testing for other atypical pneumonia (*Mycoplasma*, adenovirus, cytomegalovirus, Ebstein-Barr virus, *Chlamydia pneumoniae*) and RT-PCR for other common viruses including influenza virus, sincitial respiratory virus, metapneumovirus and human coronavirus producing common cold, also showing negative results.

Consequently, despite suspicion of COVID-19 disease, the persistent absence of microbiological confirmation and the atypical age of presentation, led us to obtain on the third day of admission a thoracic high resolution CT (HR-CT), which revealed diffuse pulmonary nodules with mediastinal widening and lytic bone lesions affecting the dorsal vertebrae, sternum and second right costal arch. These radiological findings suggested a neoformative process as an aetiological agent (figure 2).

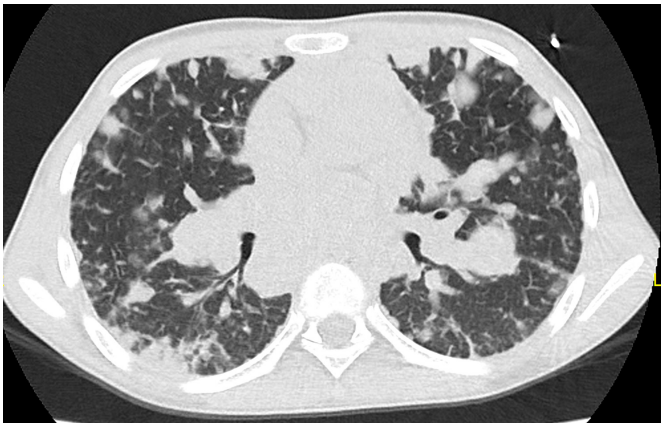

Figure 2 Chest high resolution CT. On day 3, scan showed multiple nodular adenopathies without parenchymal opacities. Mild mediastinal widening. Findings compatible with lymphatic dissemination of a neoformative process.

TREATMENT

Once the presumptive diagnosis of oncological process was set, COVID-19 targeted treatment was discontinued, and hyperhydration and rasburicase were started. The patient was transferred to a reference centre with a paediatric oncohaematology service.

Finally, after performing bone marrow biopsy that showed small, round blue cells, suggestive of solid tumour infiltration, single photon emission computed tomography (SPECT) and bone biopsy were performed. Ewing's sarcoma with metastatic pulmonary and bone marrow dissemination was then diagnosed.

OUTCOME AND FOLLOW UP

The patient improved after support at PICU and was admitted into EUROEWING 2012 trial for chemotherapy treatment. He also needed orthopaedic corset for vertebral pain stabilisation and is currently being followed outpatient.

DISCUSSION

In the context of current COVID-19 pandemic, clinicians have stated that children tend to have a more benign course when infected with SARS-CoV-2.[1] However, paediatricians have been witnessing a significant number of cases presenting with acute respiratory failure and more recently, severe Kawasaki-like syndromes.[2]

When managing a critically ill patient, the initial diagnose and treatment while awaiting definitive microbiological results, is often empirical. Since current literature is describing for teenagers and young adults a clinical scenario of hyperimmune response similar to what is being reported in the older population, most centres and national guidelines propose to apply immunosuppressors like corticosteroids and the IL-6 inhibitor tocilizumab at this critical stage of the disease.[3–5] In our case, the sudden respiratory failure with laboratory and clinical data that suggested some hyperinflammatory response with a first rapid antigen antibody test positive for SARS-CoV-2 guided the initial management, with a transitional good response. Nonetheless, the unusual follow-up course with repeatedly negative more sensitive and specific microbiological tests (RT-PCR and serological ELISA) required to perform an HR-CT scan in order to establish the aetiology of the damage to the lungs, finding none of the radiological patterns compatible with COVID-19 pulmonary disease that are being described in children (subpleural lesions, consolidation with halo sign or ground-glass opacities).[6] Initial positive rapid antibody test was considered false-positive.[7–12]

On the other hand, chest CT has been proposed as a diagnostic criterion by the National Health Commission of China in Hubei with the benefit of advancing proper treatment and isolation measures due to the delays of microbiological testing. Also, some studies have suggested that chest CT may have higher sensitivity for diagnosis of COVID-19 than RT-PCR, and may have a role as the first step in diagnosis and follow-up to clinical response.[13] Our patient's chest CT revealed pulmonary dissemination with vertebral lytic images, thus impelling us to extend the differential diagnosis to other entities like haematological or solid tumours that could present as lung metastases. Those lytic images were crucial for our diagnosis so we retrospectively reviewed with our radiology team the first plain chest X-ray images performed on our patient and could not find such lesions, perhaps hidden

behind the extensive peribronchial nodular opacities and lung parenchymal infiltration. Furthermore, a lateral chest projection was performed weeks later as part of the patient's respiratory follow-up but only indirect signs of dorsal bone infiltration were found (anterior vertebral wedging at T8–T9). In our case, the final diagnose of extended Ewing's sarcoma was set after a radiological extensive full body SPECT and bone biopsy. This is a very aggressive neoplasm with poor prognosis depending on clinical metastasis being blood dissemination the most frequent route of metastases to the lungs and bone marrow.[14]

Learning points

- In this epidemiological environment, physicians are facing clinical COVID-19 mimics that could affect or delay appropriate specific treatment for other entities such as cardiological events or even oncological debuts. We must take in mind that the laboratory findings of 'hyperinflammatory cascade' are indeed no specific for COVID-19 and some autoimmune diseases and extensive tumorous activity should be taken into consideration when facing a suspected patient with COVID-19 with an atypical clinical course.
- Plain chest X-ray may show unspecific patterns that can also be seen in other infective pulmonary diseases that are more common in children (for instance atypical pneumonia). Chest CT may help establish some hallmark COVID-19 patterns, but because of the need to avoid exposure to ionising radiation, its application in children is not well established, and should only be used when the benefits clearly overcome the risks.
- Since most of the paediatric patients are mild cases, when a paediatric patient is admitted for intensive treatment, other entities (including coinfection with other agents) must be considered without delay.
- Microbiological diagnosis poses some difficulties. First, the results obtained in the serological tests must be interpreted with caution, especially those based on rapid antibody detection that may cross-react with other pathogens, including other human coronaviruses giving false-positive results. Also, reverse transcription PCR can be affected by patients' viral load and improper clinical sampling, what is not unusual in children.

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