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RESEARCH ARTICLE

UNCOMMON PRESENTATION OF COVID-19 IN A CHILD: ASSOCIATION OF MIS-C WITH NECROTIZING PNEUMONIA AND SPONTANEOUS PNEUMOTHORAX

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ABSTRACT

Introduction: The novel SARS-CoV- 2 virus have rapidly spread in the past year throughout the world and became a pandemic. Pediatric cases of COVID-19 are often mild or asymptomatic, accounting for less than 1% of critical cases (Zimmermann P, 2020). **Case presentation:** We describe a case of a 13-year-old boy with COVID-19 who had an unusual presentation of the disease with hemoptysis, that subsequently developed multisystem inflammatory disease temporally associated with COVID-19, with decrease of T cell subpopulations, bacterial superinfection, necrotizing pneumonia, and spontaneous pneumothorax. This case is to provide details about less usual and very severe course of the COVID-19 disease for the clinicians who manage children with SARS-CoV-2 infection. **Conclusion:** Although uncommon, severe evolution of Covid-19 in pediatric patients should be taken into consideration and further clinical studies are needed asses the real impact on child health and to elucidate the best clinical and therapeutic approach.

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INTRODUCTION

The novel SARS-CoV-2, which causes the disease called COVID-19, has rapidly spread across the globe. As of march, over 11 million children have been tested positive for COVID-19 since the onset of the pandemic (state data report, 2021). Pediatric cases of COVID-19 are often associated with mild illness or an absence of symptoms, with critical pediatric cases causing multiple organ dysfunction syndrome in less than 1% of patients (Zimmermann P, 2020). In addition, the increasing global recognition of multisystem inflammatory syndrome in children (MIS-C) as an important cause of COVID-19 related morbidity and mortality in children must not be underestimated, necessitating early diagnostic and management (Gray *et al.,* 2020). We describe a case of a pediatric patient with COVID-19 who initially presented to the emergency department with cough and hemoptysis and who developed MIS-C with decrease of T cell subpopulations, myocarditis, bacterial superinfection, necrotizing pneumonia, and spontaneous pneumothorax.

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We describe this case to provide information for clinicians who manage children with SARS-CoV-2 infection.

CASE PRESENTATION

A 13-year-old male presented to the hospital with a 2-days history of hemoptysis. He also complained of low-grade-fever, sore throat, spastic cough, chest pain, shortness of breath, noisy breathing, headache, and fatigue. The symptoms developed gradually, with an onset 3 days prior to the admission. Nasopharyngeal swab tested for SARS-CoV-2 using real-time polymerase chain reaction returned positive.
He was otherwise a healthy child with normal growth and development. Family history was positive for TB infection (mother). Therefore, the patient had a regular follow-up, with Mantoux testing and chest X-ray being done periodically. Physical examination revealed a severely ill, anxious patient with a low-grade fever (37.3°C), tachycardia, increased work of breathing, acrocyanosis and oxygen saturation of 88% on room air. At the examination of respiratory system, diminished vesicular breath sounds were noted on the right side. Also, widespread expiratory wheezes were present. Abdominal examination showed moderate hepatomegaly. The examination of other systems was unremarkable. On the first

day of admission, the chest radiographs were abnormal with (Figure 1).

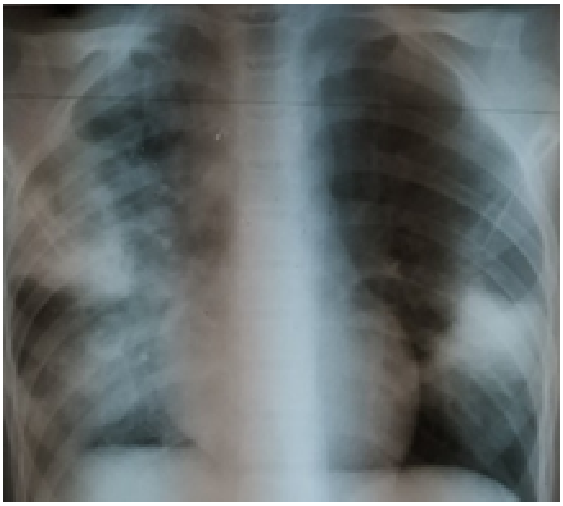

Figure 1.

On the following 2 days his condition was worsening. He complained of chest pain, mostly in right posterior region, myalgia, cough with bloody and mucopurulent discharge. He continued to have fever up to 38,0 °C and with an oxygen saturation of 95% with 5 L/min of oxygen. Nevertheless, when the patient was changing his position, he was having desaturations and signs of respiratory distress. A second X-Ray showed more lung involvement with a progression of patchy areas of pulmonary infiltrate, with pleural thickening on the right with Brixia score of 15 (9/6) and sings of cardiac disease (Figure 2).

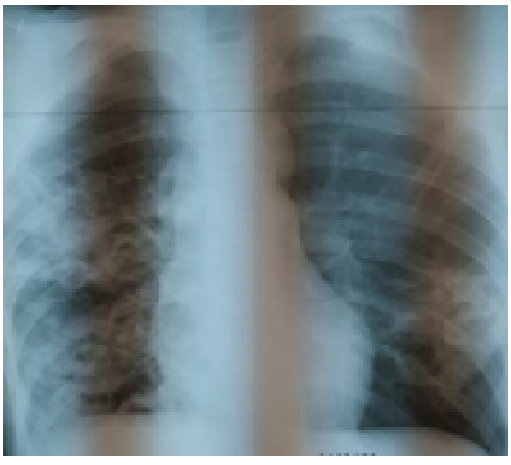

Figure 2.

Bilateral polysegmental pneumonia An extensive work-up was done, revealing anemia (hemoglobin of 110 g/L and hematocrit of 35.7%), leucocitopenia-2,9x10^9 leukocytes (82% polymorphonuclear) with only 15% lymphocytes, polymorphonuclear/ lymphocyte ratio >3 (5,4). Also, the patient had a marked inflammatory state with an erythrocyte sedimentation rate of 30 mm per hour, C-reactive protein of 192 mg/L, and D-dimer of 4,04 µg/ml, high ferritin (216,2 ng/mL), procalcitonin (22,29ng/ml), fibrinogen (10,6g/L), aPTT (21,1 sec), and hypoproteinemia (54,5g//l), hypoalbuminemia (27,9 g/L), hypocalcemia (2,02 mmol/l). Septic workup (urine culture, blood culture) was negative. Empirical antibiotics included ceftazidime, amikacin, hormonal treatment, and anticoagulant therapy were initiated. Also, due to negative evolution, a chest CT was done, that showed consolidation in the right lung associated with loss of lower lobe volume and partial loss of middle and upper lobes suggesting atelectasis. The presence of destructive elements in the right lung suggested necrotizing pneumonia with cavitary necrosis. On the left a polysegmental pneumonic infiltration, with atelectatic component was also noted. Microcalcinates were presented in the right hilum (TB sequelae?). Sputum analysis for BAAR, GeneXpert and Mantoux reaction were negative, and the diagnosis of acute pulmonary tuberculosis was ruled out. A study of the child's immune status showed total lymphocytes (0,313), CD4+(0,227), CD8+(0,08), NK (0,033) below the normal range, along with antibody-secreting lymphocytes (0,283), resulting in the total failure of the innate and adaptive immune response. Metronidazole was added to the treatment, so the child continues mask oxygen therapy, antibacterial, steroid medication, fresh frozen plasma, anticoagulant therapy and symptomatic treatment.

The next 5-6 days the child's condition got better, blood tests confirming the improvement with a decrease in inflammatory markers including neutrophilia, the erythrocyte sedimentation rate, C-reactive protein, fibrinogen. However, periodically the patient presented bradycardia combined with abnormal ECG, and with a rise in cardiac inflammatory markers: D-dimer (6,61 µg/ml), troponin T (5,38pg/ml) that suggested the presence of acute myocarditis. At day 10 after admission, patient condition worsened dramatically. He became tachypneic, started to have episodes of mild hypoxia. His cough got worse, and he had severe pain in the right hemithorax, that pushed the patient to have a forced position. Laboratory tests showed leukocytosis (12.9x10^9/l), marked deviation of the formula to the left (myelocytes -1%, metamyelocytes -2%, bands - 5%, neutrophilia -87%, erythrocyte sedimentation rate 6mm/hour. Sputum bacteriology at that point showed the presence of Str.viridans 10^6, St. aureus 10^4, and respiratory panel (PCR) pointed to the presence of Enterovirus and Rhinovirus. A second sputum culture showed the presence of Cryptococcus, thus indicating viral, bacterial, and fungal superinfection. The chest radiography done at same day showed signs of spontaneous pneumothorax on the right with collapse of the upper and middle lobe segments, without displacement of the mediastinum. The progression of pneumothorax in the following radiographs lead to microthoracotomy and insertion of the ***Bülau***-Drain (Figure 3).

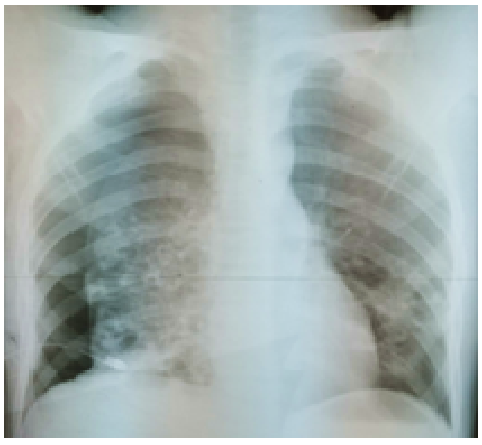

Figure 3.

At that point, the treatment consisted of antibacterial therapy - i/v (Meropenem, Vancomycin), Fluconazole i/v (considering the presence of cryptococcus); Heparin, Methylprednisolone (tapering dose regimen), plasma; fluids, oxygen, and symptomatic therapy. Despite to lack of fever and improvement of the toxic syndrome, the child's condition remained profoundly serious due to respiratory failure, desaturations, forced position, and shallow breathing. The right side of the chest almost did not participate in the act of breathing. Nine days after the chest tube placement, pneumothorax persisted. Thus, he was transferred to the surgical unit of our hospital for further treatment, with a gradual improvement of his condition. Repeated chest radiographs showed a marked reduction of free air in pleural space on the right and re-expansion of the lung (Figure 4).

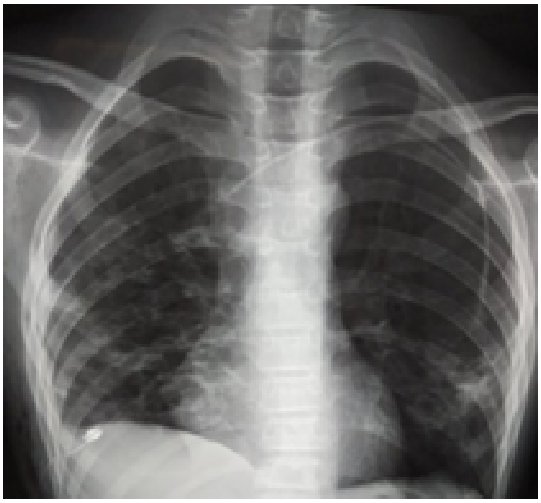

Figure 4.

The right lung volume was decreased, and multiple pseudo cavities were seen on the whole area of the right lung and S4 and S6 on the left. With a diagnosis of severe form COVID-19 and pulmonary sepsis (St. Aureus) the child was discharged home 35 days after admission.

DISCUSSION

Coronaviruses are well-known human and animal pathogens. The novel SARS-CoV- 2 virus has rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. According to the last data (March 2021), over 11 million children have tested positive for COVID-19 since the onset of the pandemic (state data report, 2021). Still, pediatric SARS-CoV-2 infections are not well understood, regarding the relative susceptibility to infection and the amount of virus shed by children (Sette A, 2021). Pediatric cases of COVID-19 are often associated with mild illness or an asymptomatic form, with critical cases causing multiple organ dysfunction syndrome in less than 1% of patients (Zimmermann P, 2020). It remains a mystery why the mortality and morbidity are lower in children, as compared with adults (Bai K,2020; El Dannan H,2020). Although mainly a respiratory disease, COVID-19 is considered a multisystem disease and has multiple clinical manifestations (Gray D,2020; Kosmeri C, 2020). The most common symptoms in children with acute SARS-cov-2 infection (COVID-19 disease) described in literature are fever and rhinorrhea, or congestion, myalgia, headache, fatigue, and gastrointestinal symptoms including nausea, vomiting, or diarrhea (Rubens, 2021).

This patient presented with initial clinical manifestations of cough associated with hemoptysis (Shi. To date, hemoptysis has been rarely reported in patients with COVID-19 infections. In previous new emerging coronavirus infections such as MERS and SARS, hemoptysis has never been mentioned. From summarizing of available published data on patients with COVID-19 from China, only 1.43% patients present hemoptysis (Shi F.,2020). The origin of hemoptysis in our patient is not very clear. Even though at the time of hospitalization acute TB was excluded in our patient, we cannot rule out the role of a specific process in hemoptysis in him, considering the child's contact with the mother, who suffered TB infection and the presence of microcalcinates in hilum of the right lung, evidenced by pulmonary CT. There are insufficient data on covid-19 and TB infection or supported TB infection in children. The data from literature does not indicate TB being a major risk factor for COVID-19 death in children, however, analyses of data are ongoing (Gray D,2020). In addition, the implications of previous TB disease and current co-infection with TB for severe COVID-19 in children requires further studies. At least, medical workers in high burden areas must perform standard screening of TB in children with the respiratory tract illness, in addition to COVID-19 testing (Gray D, 2020).

Another feature of the presented case is the appearance of spontaneous pneumothorax on the right on the 10th day of the disease which appears to be rare in children affected by SARS-CoV2 infection. From presented data, children with MIS-C were statistically more likely to have pleural effusions and interstitial opacities on chest radiography, but pneumothorax was not present on any chest radiographs in 51 investigated children (Biko DM,2021). Regarding the laboratory tests, our patient had anemia, leukopenia, neutrophilia and lymphocytopenia. According to literature data, in COVID-19, lymphocytopenia is common and correlates with severity of disease. SARS-CoV-2 infection is associated with CD4+ and CD8+ T cell lymphopenia (Sette A,2021; Bai K,2020). The reason of the lymphocytopenia associated with SARS-COV2 infection remains largely unknown. The low levels of expression of the viral entry receptor into the immune cell compartment disprove the idea that lymphocytopenia is the result of a direct interaction between the virus and the lymphocytes (Belaid, 2021). Therefore, it is more plausible to assume that lymphopenia is a direct consequence of significant cell migration to the site of infection, where the immune response is initiated (Belaid, 2021). Different studies have demonstrated that in patients with severe form of COVID-19, total lymphocytes and especially CD4+, CD8+ T cells and B cells were significantly lower than those in patients with the mild forms (Rahi MS,2021; Corrao, 2021). In cases where the total number of lymphocytes and CD8 + is below normal, and the total number of B-lymphocytes and NK-granzyme is within normal limits, there is a partial compromission of the adaptive immune response. When total lymphocytes, CD4+, CD8+, NK and NK lymphocyte granzymes are <50% below the normal range, it results in the total failure of the innate and adaptive immune response and severe form of Covid-19(Rahi MS,2021). Low levels of CD3+, CD4+, CD8+, CD16+, CD19+ T cells in our children, increased CD4/CD8 ratio, were important factors for the development of a severe form of the disease. However, the underlying mechanism for T cell reduction in COVID-19 patients remains unclear and requires further research (Liu, 2020).

Even though the exact sequence of events has not been elucidated, the impaired immunological process, starting at the border between the alveoli and the lung endothelium, apparently determines the local activation of hemostatic processes leading to the deposition of platelets, neutrophils and fibrin (i.e., micro- and macrovascular pulmonary thrombosis), which probably contributes to general respiratory failure, systemic spread of inflammation and coagulopathy (Del Borrello, 2021). Because of lymphopenia, the neutrophil/lymphocyte index was significantly increased in our case (5.4). Similar data was presented in studied literature sources, that demonstrated a significantly lower lymphocyte level and increased neutrophil-to-lymphocyte ratio in those with a critically ill patients (Rahi MS, 2021). Along with multiple other serum markers, lymphocyte count and the neutrophil-to-lymphocyte ratio have been proposed as prognostic factors for disease severity and outcome in adults (Rahi MS, 2021). Low lymphocytes, increased levels of neutrophils, CRP, erythrocyte sedimentation rate, procalcitonin, fibrinogen, D-dimer, ferritin, LDH, fever lasting over the 3 days, SARS-CoV-2 positive at swab testing and serology, satisfy diagnostic criteria of multisystem inflammatory syndrome temporally associated with SARS-CoV-2 in our child (Rubens J,2021; Kest H,2020). Available literature shows that our knowledge of MIS-C is largely incomplete. According to literature, a small proportion of children go on to develop multisystem inflammatory syndrome (MIS-C)(Rubens J,2021; Kest H,2020). The prevalence of MIS-C in communities experiencing wide-spread COVID-19 infections is unclear but has been estimated at 2/100,000 children (A Yasri, 2020). The development of MIS-C in close association with SARS-CoV-2 infection appears to be well-documented and, in most cases, can be considered a post-infectious manifestation secondary to an abnormal immune response (Esposito S, 2021). However, in some cases (as well as in the case described by us), the clinical picture with symptoms of MIS-C develops during the acute phase of SARS-CoV-2 infection, and these manifestations may be associated with direct damage of the virus (Esposito S, 2021).

Although there are hypotheses about risk factors for developing MIS-C in children, such as lower pre-existing immunity to coronavirus, specific risk factors for developing MIS-C in children are not well estimated (Esposito S,2021; A Yasri,2020). Research shown that children who develop severe COVID-19 often have one or more underlying conditions, including obesity, asthma, sickle cell disease, and immunosuppression (Rubens J,2021). The wide spectrum of clinical manifestations of SARS-CoV-2 disease suggests that individual immune responses to SARS-CoV-2 play a critical role in determining the clinical course after primary infection (Carsetti, 2020). Our patient shown signs of bacterial super infection after 10 days of being ill. However, the mechanisms of bacterial-SARS-CoV-2 coinfection require further study. An evoked adaptive immune response to viral infection has been shown to block the host's innate immune response against bacterial infection. This fact can explain why bacterial co-infections occur when the virus starts to be eradicated in patients with COVID-19 and in our patient too (Mirzaei R, 2020).

CONCLUSION

Further clinical studies are needed to improve the definition of multisystem inflammatory response in children, its predictors and pathogenesis, the real impact on child health and to elucidate the best clinical and therapeutic approach. We hope that this article will contribute to future clinical trials analyzing the course of COVID-19 in children by describing an unusual course of the disease, combining the presence of a multisystem inflammatory response in the acute phase of the disease, the presence of spontaneous pneumothorax and association of superinfection with multiple pathogens.

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