A severe case of COVID-19 in an adolescent with PIMS-TS, cardiomyopathy, and pulmonary embolism.

ABSTRACT

We report the case of a 14-year-old male patient with no previous history of cardiovascular disease or thromboembolic episodes, admitted to our hospital with a severe form of COVID-19, in the 9th day of disease evolution, with acute respiratory and heart failure symptoms. Chest computer tomography showed bilateral multilobular ground-glass opacities, consolidations, and a sub segmental arterial branch thromboembolism. The echocardiography showed a dilated left ventricle with severely impaired left ventricular function (LVEF=30%) . Blood test showed extremely elevated NT pro-BNP (22 558 ng/L), inflammatory markers and D-dimers. The diagnosis of PIMS-TS, COVID-19 sepsis-related cardiomyopathy and pulmonary thromboembolism was made, with a favourable outcome under supportive treatment. Clinicians should be aware of this severe presentation of COVID-19 in children.

INTRODUCTION

COVID-19, the most important pandemic of the 21th century, is now responsible for more than half a million deaths worldwide. Children are less likely to become severely ill compared to adults, but there is still emerging data of pediatric SARS-CoV2 associated disease.[1] Respiratory symptoms are the most commun clinical findings related to COVID-19, but thromboembolic manifestations and cardiac involvement have been lately discribed as severe complications and as factors incresing mortality risk.[2,3] Still, very few clinical cases have been reported until now regarding cardiac or thromboembolic complications associated with COVID-19 in children. [3,4,5.]

CASE REPORT

A previously healthy 14-year-old caucasian boy (height 180 cm, weight 70 kg) presented to our hospital with a 9-day history of fever, sore throat, headache, coughing, abdominal pain and nausea. He has been close contact with a COVID-19 confirmed patient and his PCR SARS-COV2 test was positive in a county hospital one day before transfer and admission into our tertiary care hospital.

On physical examination, he was in respiratory distress, dyspnoeic and tachypneic. His peripheral oxygen saturation (SpO2) was 88%, his respiratory rate was 38 bpm, his heart rate 112 bpm and blood pressure was 80/51 mmHg. With high flow oxygen (10 L/min) his SpO2 improved at 96%. The blood tests showed leucocytosis (14,000/mm3) with neutrophilia (88%) thrombocytopenia (114,000 mm3) increased C-reactive protein (251 mg/l) , procalcitonin (10,41 ng/ml), fibrinogen (734 mg/dl), impaired renal function (urea 63 mg/dL), hepatic cytolysis (glutamic oxaloacetic transaminase 54 U/L, glutamic pyruvic transaminase 60 U/L), increased NT-pro BNP 22 558 ng/L with normal Troponin I 0,03

ng/ml) , elevated D-Dimers 2659 ng/mL, LDH = 300 U/l. IL-6 performed the next day was normal, TNF-alfa was 0 pg/ml, PAI-1 = 795,1 ng/ml.

Table 1. Laboratory results.

The echocardiography revealed dilated left ventricle (end diastolic diameter 60 mm) with severely impaired systolic function (LVEF = 30%), global hypokinesia, moderate - mitral regurgitation. In addition there was a dilated right ventricle (basal diameter 41 mm), severe tricuspid regurgitation, tricuspid annular plane systolic excursion (TAPSE) of 17 mm, with probable pulmonary hypertension. There was no pericardial effusion. EKG showed a slightly T wave flattening.

His pulmonary chest scan showed bilateral multilobular ground-glass opacities and consolidations, involving partially the upper lobes and in totality the lower lobes. Also observed was thromboembolism involving the subsegmental arterial branch of the posterior basal right lower lobe.

Figure 1,2: Comparative pulmonary chest scans, day 1 versus day 10, showing bilateral multilobular ground-glass opacities and consolidations, involving the upper lobes (fig. 1) and lower lobes (fig.2), and important regression of the condensation areas after 10 days.

Two PCR-SARS COV2 tests performed at 24 h distance, in our hospital, were negative, but the SARS-COV2 antibody rapid test was positive for IgG, and slightly positive for IgM.

He was admitted to the intensive care unit where he received antibiotic treatment (Meropenem + Linezolid – for a total of 21 days), dexamethasone (starting 16 mg/day, doses gradually reduced), albumin and high flow oxygen (for 5 days). For the acute heart failure with hemodynamic instability he received dobutamine (for 5 days) , furosemide and spironolactone.

Screening for other infectious pathogens was negative. Nasopharyngeal PCR for adenovirus, Coronavirus 229E, HKU1, NL63, OC43, metapneumovirus, rhinovirus/enterovirus, influenza A, influenza B, parainfluenza- 1,2,3,4, SRV, Bordetella parapertussis, Bordetella pertussis, Chlamydia pneumonie, Mycoplasma pneumonie. Throat culture, nasal culture, urine culture, blood culture, were negative. Serology for HIV, hepatitis B and C were negative. Drug use test was negative.

Day 4 echocardiography revealed improvement of the heart function (LVEF= 50% under inotropic treatment) with no pulmonary hypertension.

Day 10 chest scan shows important regression of the condensation areas, with small areas of atelectasis latero-basal bilaterally. Partially regression of the thromboembolic affected area previously described.

Day 14 follow-up echocardiography revealed total recovery of the heart function, with normal LVEF, no wall motion abnormalities, normal sized cardiac chambers, no valvular regurgitation, no pulmonary hypertension.

At day 21 the patient was transferred to a paediatric cardiology ward, for further investigations regarding thromboembolic predisposing diseases, starting of oral anticoagulant therapy and further cardiologic follow-up.

DISCUSSION

We report a case of sever COVID-19 infection in an adolescent, with life-threatening PIMS-TS, COVID-19 sepsis associated cardiomyopathy, pulmonary thromboembolism and bilateral extensive pneumonia. We had to make a differential diagnosis with implications in the acute treatment and expected outcomes.

The disease was initially with mild evolution, but after 8 days of constitutional symptoms, upper and lower respiratory symptoms and gastrointestinal symptoms, treated at home only with symptomatic treatment (paracetamol), there was a late-onset of severe complications in the 9th day, with rapidly development of acute respiratory and heart failure symptoms.

After an initial positive RT-PCR SARS-CoV2 test in a county hospital, during hospitalisation in our clinic he had multiple negative RT-PCT SARS-CoV2 tests, but positive rapid antibody test for specific IgM and IgG, as he was already in a later stage in the disease evolution.

As we know, there are fewer data for pediatric COVID-19 cases available, compared to adults. However, the data suggest less severe symptoms than adults and lower mortality. In the Dong and al. study, from China, in a cohort of 2135 paediatric patients, more than 90% were asymptomatic, mild or moderate cases.[1] The data from USA is similar, from the total number of COVID-19 patients, only 1,7% were < 18 years. From a total of 745 cases with known hospitalisation status, just 147 were hospitalised, and 15 (2%) were admitted to an ICU. From the total USA cohort of 2575 pediatric cases there were 3 deaths, still under investigation.[6] In the EU/EEA and the UK, children made up a very small proportion of the 744 448 cases, the proportion of cases hospitalised were lowest in the age groups 5–11 years and 12–18 years (3% and 4% respectively) and highest among 0–4 year olds (10%). Deaths among cases under 18 years were extremely uncommon; only six out of a total of 19 654 (0.03%).[7]

In the paediatric population, several countries have reported clusters of children and adolescents requiring admission to intensive care units, with a multisystem inflammatory condition with some features similar to those of Kawasaki disease and toxic shock syndrome. A possible temporal association with SARS-COV-2 has been hypothesized because the children were positive for SARS-CoV2 infection by polymerase chain reaction (PCR) or serology. The World Health Organization (WHO) has published in May, preliminary case definitions for the Pediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 (PIMS-TS) . This include children and adolescents 0–19 years of age with fever $\geq$3 days and two of the following - Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); Hypotension or shock ; Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP); Evidence of coagulopathy (by PT, PTT, elevated d-Dimers); Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain) - and elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin - and no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes - and evidence of COVID-19 **(**RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19. As we can see, out patient can be diagnosed with PIMS-TS, he had fever for more than 3 days, hypotension, features of myocardial dysfunction, evidence of coagulopathy, acute gastrointestinal problems, elevated

markers of inflammation and no other obviouse microbial cause was found, and he was RT-PCT SARS-COV2 positiv, also with positive serology.

Our patients severe form of COVID-19 was complicated by the development of acute heart failure with severely impaired left ventricular function (LVEF=30%) and very high NT-proBNP levels, related to a COVID-19 severe infection.

The exact pathogenesis of cardiac involvement in COVID- 19 is not entirely clear. Several mechanisms of cardiac damage are likely to be involved, including direct viral myocardial damage hypoxemic injury caused by respiratory failure, the prothrombotic state caused by severe systemic inflammation, ischemia from myocardial supply-demand mismatch and indirect injury mediated by cytokines secondary to systemic inflammation.[9] Some studies estimate that acute cardiac injury (elevation of cardiac biomarkers to >99th percentile of the upper reference limit and electrocardiographic and echocardiographic abnormalities) occurs in 7-17% of hospitalised patients, being significantly more common in patients admitted to ICU and among those who died.[10]

We had to make a differential diagnoses between two COVID-19 possible cardiac complications, myocarditis and sepsis-related cardiomyopathy.

The prevalence of myocarditis among COVID-19 patients is unclear, due to lack of specific diagnostic modalities to assess myocarditis, many cases being assumed and not based on confirmatory diagnoses. In the cases published until now, elevation of both troponin and NT-proBNP levels were observed in the COVID-19-related myocarditis. Although a negative troponin result cannot exclude myocarditis, negative serial high-sensitivity cardiac troponin still is helpful in the acute phase and makes diagnosis of acute myocarditis significantly less likely.[9]

In the case of our patient, he had constant normal levels of troponin, but very high NT-proBNP levels, making the diagnosis of myocarditis less likely, so we continued our differential diagnosis with sepsis-related cardiomyopathy .

Sepsis-related cardiomyopathy is a disease characterised by reversible myocardial dysfunction in which the myocardial injury is thought to arise from increased nitric oxygen production suppressing the cardiomyocyte's response to calcium and downregulating the heart's β1-adrenergic receptors. The main characteristics of sepsis-related cardiomyopathy are left ventricular dilatation, impaired ejection fraction and recovery in 7-10 days.[11] A case series study showed that 67% of critically ill COVID-19 patients required vasopressor and that 33% developed probable sepsis-related cardiomyopathy.[12]

Our case complied with all of the characteristics specific a COVID-19 sepsis-related cardiomyopathy, he had left ventricular dilatation (end diastolic diameter 60 mm), impaired ejection fraction (LVEF=30%) and recovery of heart function already after 4 days of supportive treatment, with normal echocardiography at day 14. We concluded sepsis-related cardiomyopathy as our final diagnosis.

The implication of the differential diagnosis of the cardiac complications of COVID-19 may also lie in the possible different late complications. The long-term effects of healed myocarditis are unknown, still there is the possibility that some of the patients may be at risk of arrhythmias. In a study of patients with active and healed myocarditis, monomorphic

ventricular tachycardia and regular ventricular arrhythmias were more frequent in those with healed than acute myocarditis.[9] On the other hand sepsis-related cardiomyopathy is a reversible myocardial dysfunction without production of cardiac necrosis. It is self-limited but could lead to decreased ventricular compliance depending on the length and intensity of the disease and the quality of the myocardium at the moment of injury.[13]

On the other hand, our patient with no high risk factors for pulmonary thromboembolism (PTE) , developed a sub segmental arterial branch thromboembolism in the context of sever COVID-19 disease. He presented, as previously mentioned, with high D-dimers, modified prothrombin time and low platelet count. It was a minor PTE, but in the context of multiple cardiac injuries, it could also have contributed to the acute heart failure, making the differential diagnosis more challenging.

We know that COVID-19 has been associated with a hypercoagulable state. The International Society of Thrombosis and Haemostasis (ISTH) advocates the use of laboratory tests , including D-Dimers , prothrombin time and platelet count, to stratify patients at risk of increased blood clot formation. The incidence of acute pulmonary embolism in patients diagnosed with COVID-19 is currently unknown.[14] This, to our knowledge, may be the first published case report of a child with pulmonary thromboembolism complicating COVID-19.

PTE in the paediatric population is relatively rare when compared to adults. It is critical to maintain a high index of suspicion of PTE particularly among patients at greatest risk, including patients with a central venous line, congenital heart disease or other conditions known to predispose to PTE (coagulation disorders, obesity, hormonal supplementation etc.).[15] Recommendations for treatment of the paediatric patients have been extrapolated at first from adult data, with some recent Consensus- Based Clinical Recommendations being published recently, regarding anticoagulant thromboprophylaxis in children hospitalized for COVID-19 related illness. They suggest anticoagulant thromboprophylaxis be administered in children hospitalized with COVID-19 related illness (including PIMS-TS) who have superimposed clinical risk factors for hospital-associated VTE (venous thromboembolism) or markedly elevated plasma D-Dimer levels ($\geq$ 5 times the upper limit of normal values), in the absence of contraindications. The risk factors for hospital-associated VTE includ : central venous cathether, mechanical ventilation, prolonged lenght of stay (anticipated > 3 days), complete immobility (Braden Q Mobility Score= 1), obesity (BMI > 95th percentile), active malignancy, nephrotic syndrome , cystic fibrosis exacerbation, sickle cell disease vaso-occlusive crisis, or flare of underlying inflammatory disease (lupus, juvenile idiopathic arthritis, inflammatory bowel disease), congenital or acquired cardiac disease with venous stasis or impared venous return, previous history of VTE, first degree family history of VTE bedore age 40 years or unprovoked VTE, known thrombophilia (protein S, protein C or antithrombin deficiency, factor V Leiden, factor II G2010A, persistent antiphospholipid antibodies), pubertal – post pubertal – or age > 12, receving estrogen-conteining oral contraceptive pill, status-post splenectomy for underlying hemoglobinopathy. As prefered option for anticoagulant thromboprophilaxis in children hospitalized with COVID-19 related

illnesses they suggest low-dose LMWH subcutaneously twice-daily, targeted to achiev a 4 hour post-dose anti-Xa activity level of 0.2- <0.5 U/ml, in children who are clinically stable without severe renal imparment, in the absence of contraindications.[16]

In the case of our patient we immediately decided to start anticoagulant thromboprophylaxis, with the use of LMWH in therapeutic dosages of 0,6 mg x2 /day subcutaneous, for a total of 21 days, followed by post- discharge from hospital, oral anticoagulant therapy with acenocumarol with a duration that may vary from 3 months to 1 year. Coagulation disorder check-up is next in plan for him.

No other viral respiratory infection has been determined, until now, with having a greater frequency of association with pulmonary thromboembolism. Further studies are needed regarding association between PTE and COVID-19.

Our patient, under supportive treatment for acute respiratory and heart failure, had a favourable outcome.

CONCLUSION

We report the case of a sever COVID-19 infection in an adolescent, with life-threatening PIMS-TS, COVID-19 sepsis associated cardiomyopathy, pulmonary thromboembolism and bilateral extensive pneumonia. In the context of the current state of knowledge regarding paediatric COVID-19, showing usually less sever cases and less mortality than adults, we state that clinicians should be aware of this possible severe presentation of COVID-19 in children. There is a need for further research to better understand the pathogenesis and frequency of cardio-vascular involvement in the paediatric populations.

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