

CASE REPORTS

PEDIATRIC MULTI-SYSTEMIC INFLAMMATORY SYNDROME COMPLICATED BY SEVERE CARDIAC AND RENAL INVOLVEMENT

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ABSTRACT

Pediatric inflammatory multisystemic syndrome (PIMS) is a new, rare and serious complication described in children and adolescents after SARS-CoV-2 infection. This emerging disease is responsible for a myocardial damage of variable severity at often complicated by a state of cardiogenic shock. It's very particular by the vasoplegia and associated with a diastolic arterial hypotension. We report two cases of pediatric multisystemic inflammatory syndrome, which complicated by severe cardiac involvement, and associated with renal involvement, that making the management more delicate. Our objective is to determine the clinical, biological, and evolutionary particularities of the myocarditis of the pediatric multisystemic inflammatory syndrome, which is temporally associated with SARS-CoV-2 (PIMS-TS) as well as the difficulties of the management of this syndrome, that are associated to the cardiac and renal involvement. In conclusion, mortality in children with COVID-19-associated PIMS with severe cardiac involvement is rare thanks to the diagnosis and early management of these patients which is based essentially on the combination of immunoglobulin and corticosteroid therapy.

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Introduction

Pediatric inflammatory multisystemic syndrome (PIMS) is a new, rare and serious complication described in children and adolescents after SARS-CoV-2 infection. It's an emerging disease which characterized by highly variable clinical pictures resembling Kawasaki syndrome, a disease known to pediatricians and responsible for acute inflammation of the blood vessels. It is responsible for a myocardial damage, that often complicated by a state of cardiogenic shock, and very also particular by the vasoplegia, which associated with a diastolic arterial hypotension.

Case Report

Case Presentation 1

A 6-year-old boy with a history of risky contact with a member of his family who tested positive for SARS-COV 2 21 days before his admission to the pediatric ward 1 unit covid19 for a generalized febrile rash with a dry cough evolving over four days and complicated 24 hours before his admission by dyspnea. The examination on admission found a conscious, altered, irritable child, tachycardia at 168 bpm, normotensive at 100/60 mmHg, polypneic4 at 0cpm, SaO2 97% in the open air, febrile at 38.5°, and a borderline skin recoloration time to 5 seconds .he has bilateral conjunctivitis with cheilitis and a maculopapular rash (face, abdomen, back, seat and

extremities) without desquamations or adenopathies or other associated signs., in the biological assessment, he had a major inflammatory syndrome; CRP at 275 mg/l (0.3-6.0mg/l); D-dimer at 6328 ug/l, (<280ug/l); ferritinemia at 5770ng/l (40-230); fibrinogen at 5.95 g/l (2-4g/l), troponin = 100.7ng/l(<19.8ng/l).. At the blood count a hyperleukocytosis at 26000 with neutrophils at 23270 cells/ml without lymphopenia nor thrombocytopenia (leukocytes at element/ul1510; platelets at 137000element/ul) with a correct renal function (urea= 0.3g/l ; creat=6.1mg/l)and at the hydro-electrolyte balance an isolated hyponatremia at 123mEq/l .The ECG revealed a sinus tachycardia with an echocardizer, and myocarditis with a Left Ventricular Ejection Fraction (LVEF) at 28% that associated with a systolic dysfunction of the right ventricle and a multiple valvular leakages, in addition to a PAH at 40 mmHg. The left coronary is normal while the right is slightly dilated to 3.1 mm. The COVID 19 PCR came back negative with positive SARS COV2 serology (IgG = 16.34 IU/ML IgM=1.70 IU/ML). Chest radiography was normal. The diagnosis retained was a pediatric multisystemic inflammatory syndrome with severe cardiac involvement. The patient was put on immunoglobulin 2g/kg over 48 hours associated with intravenous boluses of methylprednisone 30mg/kg/day for 3 days then 2mg/kg/8h for 5 days with an oral relay at 2 mg/kg/day of Prednisone with Tapering the dosage over 4 weeks of 0.5 mg/kg/week ; and an anti-aggregating agent (acetylsalicylic acid) 100 mg/kg/day in 4 doses for 10 months, heparin therapy (LMWH) at a preventive dose 0.1mg/kg/day It's also linked to the treatment of the cardiac disease (double diuretics; ACE inhibitors and a beta-blocker) and an antibiotic

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therapy (3rd generation cephalosporin+Azythromycin). The evolution was marked at the second day of hospitalization by the onset of an acute renal failure which worsened quickly (creatinine = 61mg/l;urea= 2,34g/l) with anuria. The child was transferred to the intensive care unit where he received a session of peritoneal dialysis with administration of a bolus of corticosteroid therapy at 30 mg/kg/d. The evolution was favorable with normalization of the renal function at the fifth day of hospitalization as well as a normalization of the Left Ventricular Ejection Fraction to 89% at the control echocardiogram on the 8th day of hospitalization.

Case Presentation 2

A 14-year-old boy, with no history of contact with any confirmed or suspected COVID-19 in his family, admitted for a generalized febrile rash with respiratory distress evolving 24 hours before his admission. The examination on admission found a conscious, eutrophic, altered, irritable child, hemodynamically unstable with tachycardia at 125 bpm, hypotension at 70/90 mmHg, polypnea at 60 c/min, with signs of respiratory struggle (subcutaneous respiratory distress), oxygen saturation SpO₂ on room air was 91%, skin recoloration time 5sec and fever at 38.5°, with bilateral conjunctivitis and diffuse maculo-papular rash without desquamation or adenopathies or other associated signs. The patient was transferred directly to the intensive care unit. On the biological level, CRP to 38 mg/l(0.3-6.0mg/l); D-dimer= 5487,($<280\mu\text{g/l}$);ferritinemia =3950(40-230); fibrinogen =5,02 g/l(2-4g/l), troponin =323mg/l ($<19.8\text{ng/l}$), BNP=2600pg/ml($<100\text{ pg/ml}$). At the blood count;he had an anemia at 9 g/dl normochromic normocytic with WBC= 10000 cells/ml (lymphopenia at 1320 cells/ul; PNN at 8300 cells/ul; platelets at 126000cells/ml). The child had acute renal failure (urea=1.29 g/l;creatinine =13mg/l) with isolated hyponatremia at 123 mEq/l. The ECG revealed sinus tachycardia with echocardia and LVEF at 28% associated with dilatation of the VD and mitral as well as tricuspid valve leak without causing a dilation of coronary arterioles Z-score 0.48. The COVID 19 PCR was negative with a positive SARS COV2 serology (IgG = IU/ML IgM=/ML). The thoracic CT scan showed bilateral posterior-basement condensation foci with air bronchograms. It's more marked on the left with a right pleural effusion that linked to discrete left fissure effusion. The diagnosis was a pediatric multisystemic inflammatory syndrome with cardiac involvement and acute renal failure. The patient was put on immunoglobulins 2g/kg for 48 hours associated with intravenous boluses of methylprednisone 30mg/kg/day for 3 days then 2mg/kg/8h for 5 days with an oral relay at 2 mj/kg/day of Prednisone with Tapering the dosage over 4 weeks of 0.5 mg/kg/week; an anti-aggregation (acetylsalicylic acid) 100 mg/kg/day in 4 doses for 6 months; heparin therapy (LMWH) at a preventive dose 0.1/mg/day as well as the treatment of his heart disease (double diuretic; (double diuretic; ACE inhibitors and a beta-blocker) and antibiotic therapy (C3G+Azythromycin) with a good clinical and biological evolution as well as a clear improvement in the infarction on day 6 of hospitalization.

Discussion

SARS-CoV-2 infection has spread rapidly around the world since it was first identified in China in late 2019. In April 2020, the first cases of PIMS emerged in Europe^{1,2,3,4,5}, followed by other American and English series.^{6,7}

The pathophysiology of PIMS is not well understood. It has been suggested that the syndrome results from a strong immune response to the virus. The mechanisms of this excessive immune response are unknown.⁸ The majority of published cases had positive serological tests for SARS-CoV-2 (60/69, 87%) and less frequently positive RT-PCR tests from nasopharyngeal tests (23/70, 32%), results which further confirms the hypothesis that PIMS is linked to an immune dysregulation occurring after the passage of the acute infection and this is the case for our two patients.^{8,9}

Myocarditis in PIMS results in focal or global inflammation of the myocardium, leading to necrosis and eventually ventricular dysfunction. This may be secondary to viral replication in the myocardium or a harmful indirect immune response caused by viral infection. It has been suggested that a cytokine storm can lead to increased vessel wall permeability and myocardial edema. In a recent multicenter cross-sectional study involving intensive care units in the northern United States, more than 80% of children with COVID-19 had significant underlying chronic conditions. The two children we report were relatively healthy, but they had clinical manifestations of acute myocardial failure and acute kidney injury. The rapid resolution of ventricular dysfunction under combination of immunoglobulins and corticosteroids with management of heart failure in our children also suggests that the acute heart injury seen in this syndrome is more likely to be an immune-mediated process rather than direct viral invasion, but further study is needed. In the existing pediatric literature on PIMS, acute renal failure has been reported in 2% to 8% of children with PIMS in the United States. There are currently no published reports detailing the specific presentations of renal failure in PIMS. The proposed pathophysiology of PIMS is strikingly similar to the proposed mechanism of acute renal failure in COVID-19 infections.^{10,11}

Interestingly, our two patients had both cardiac and renal involvement. This is in agreement with an American study of 186 cases⁶ where cardiac involvement was present in 80% of cases, with hypotension or shock requiring vasoactive drugs in 48% of cases. this involvement also included dilation of the coronary arteries, a phenomenon also observed in Kawasaki disease. A depressed ejection fraction and nearly 10% of children had a coronary vessel aneurysm [25]. Thus, half of the children have acute circulatory failure at the time of diagnosis or within 36 hours of hospitalization.⁶ The clinical picture can deteriorate rapidly after admission of a child with PIMS, and with the onset of hypotension or shock within 36 h of hospitalization. Therefore, patients with biomarkers of heart failure (BNP greater than 1000 pg/mL) or significant inflammation (CRP greater than 200 mg/L) should be transferred to an intensive care unit immediately. The biological assessments to be requested on admission are summarized below (Table

1). Special monitoring must be carried out on cardiac function, respiratory status, neurological status, and renal function. Note that in the absence of a positive test for SARS-CoV-2 or contact with a person with COVID-19, different diagnoses should be considered. Serology can be repeated 2 to 4 weeks later. If suspicion remains high despite negative results, serology can be repeated using a different test. Testing of household contacts may also reveal evidence of exposure.^{12,13}

Table 1. Course of action for suspected PIMS

Clinical evaluation with transfer to pediatric intensive care unit for cardiorespiratory monitoring, if necessary. Advice in a pediatric hospital at the slightest doubt.

Biological assessment:

- Complete blood count with formula.
- Blood ionogram, urea, creatinine.
- Liverfunction: ALT, ASAT, albumin, bilirubin
- Cardiac markers / troponin and NT pro-BNP
- ECGU
- Blood gases, lactates,
- Inflammation markers: CRP, procalcitonin, SV, ferritin, triglycerides; IL-6
- Coagulation: PT, fibrinogen, D-dimer
- Creatinine kinase, lactate dehydrogenase
- Blood culture
- SARS-COV-2 serology
- SARS-COV-2 PCR
- Corpo/virology for gastrointestinal symptoms

Imaging:

- Chest X-ray
- Abdominal ultrasound or CT scan in case of symptoms

Electrocardiogram Echocardiography / cardiopediatrician opinion

Early specialist advice to assist in the management

ALT: alanine aminotransférase/ASAT: aspartate amino transférase/NT pro-BNP: N-terminal prohormone of brain natriuretic peptide/ECBU: Examination of urine by chemical/CRP: C-reactive protein/V5: Sedimentation Rate/IL-6: interleukin-6/PT: prothrombin ratio/PCR: Polymerase chain reaction.

Treatment is based on intravenous immunoglobulins (IVIg) and high-dose corticosteroids.¹³

A recent article shows better efficacy, with faster recovery of cardiac function, in children treated with this combination versus IVIG alone.¹⁴ Indeed, most patients respond very favorably to both treatments. The doses of corticosteroids are identical to those recommended in severe Kawasaki disease.¹⁵ It is recommended to combine antibiotic therapy with intravenous 3rd generation cephalosporins (C3G) for the first 48 hours, until a bacteriological cause of the fever is ruled out. A few children require a second dose of IVIG or adjuvant therapies such as anakinra (recombinant IL-1 β antagonist) if there is no clinical improvement; biological and radiological after the first dose.¹⁴ Classically, an antiplatelet agent is associated for a short time, as in Kawasaki disease KD.¹³ Concerning

acute heart failure, it may require vasopressor and/or vasoactive treatment associated with or without non-invasive or invasive ventilation. The use of circulatory assistance is no longer necessary since the disease is better known and immunomodulatory treatment is codified.¹⁶

Unlike acute COVID-19 infections in adults, clinical thromboembolic events in children with PIMS are rare. However, a consensus of expert opinion has recently proposed anticoagulant thromboprophylaxis, in some children with severe COVID-19 infection, whether acute or delayed as in PIMS. Thus, hemostasis disorders leading to a very high level of D-dimers (>5 times normal) and/or the existence of thromboembolic risk factors (central catheter, mechanical ventilation, complete immobilization, acute heart failure, obesity, underlying pathology at risk, history of thrombosis, puberty) should lead to anticoagulation in the absence of contraindications. The use of low molecular weight heparin (LMWH) at low doses, by subcutaneous route, twice a day, is proposed with an anti-Xa activity objective of 0.2 to 0.5 U/mL. In case of renal insufficiency, unfractionated heparin should be used intravenously, with an anti-Xa activity target of 0.1 to 0.35 U/mL.¹⁷

Concerning the short-term evolution, the combination IVIG-IV corticosteroids allows a rapid improvement of the clinical state in the first 48 hours. Indeed, it is effective in more than 90% of cases. The median length of stay, in our experience, is 10 days. Patients using vasopressor or vasoactive therapy can, in most cases, be weaned quickly. Additionally, the inflammatory balance also improves within a few days and usually normalizes within a month. Thus, in our experience, normalization of cardiac function occurred within 6 days of treatment with a combination of immunoglobulins and corticosteroids. Overall mortality is low.¹⁸

Conclusion

Cardiac involvement is common in children with COVID-19-associated multisystemic inflammatory syndrome. Thus, it is a delayed immunological phenomenon which associated with inflammation following symptomatic or asymptomatic COVID-19 infection rather than direct cellular injury that caused by viral replication.^{16,18} Compared to adults with COVID-19, mortality in children with COVID-19-associated PIMS with severe cardiac involvement is rare despite multisystem involvement, very high inflammatory markers, and the need for intensive care assistance. Although much of the discussion around PIMS has focused on cardiac manifestations, pediatricians should be aware of the cardio-renal association of COVID-19. Detailed mid-and long-term followup of these different international pediatric populations will provide insight into the incidence of potential complications.

Compliance with Ethical Standards

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Conflict of Interest None

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