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Abstract

Second wave of the new coronavirus (SARS-CoV-2) has been declared throughout the world. It has been always thought that children are the least affected group. A new childhood disease, referred to as MIS-C (Multisystem Inflammation Syndrome) or PIMS-TS (Pediatric Inflammatory Multiorgan Syndrome Temporally related to SARS-CoV-2) was first recognized in April 2020. Shock and multiorgan failure affected some of those children that required intensive care; others were clinically similar to Kawasaki disease or toxic shock. The clinical evidence suggests that this inflammatory multisystem syndrome is temporally associated with severe acute respiratory syndrome corona virus 2. Many clinical uncertainties regarding this new disease rapidly became apparent in prevalence, clinical phenotypes, variable severity, clinical course, and optimal management. We aim to increase awareness of this syndrome regarding the diagnosis and management of children with suspected PIMS-TS by presenting two clinical cases and illustrating the available medical literature in regards to establishing the diagnosis and the appropriate therapeutic interventions. SARS-Cov-2 related medical impacts on children seem not well clarified yet. When a PIMS-TS case is suspected then full investigations should be done, children who have persistent fever associated with abdominal pain, diarrhea ,vomiting ,cough, neurologic symptoms should have primary blood tests to identify PIMS-TS: full blood count, CRP: C-reactive protein, BUN: Blood Urea Nitrogen, Cr: Creatinine, Electrolytes and liver function. Multidisciplinary team approach seems mandatory from the very beginning. Despite the use of IVIG in the treatment of all diagnosed cases, steroids in regular doses could be a good alternative and requires further investigative evaluations.

Keywords: *Multisystem inflammatory syndrome in children, Pediatric inflammatory multisystem syndrome, Severe acute respiratory syndrome 2, MIS-C.PIMS, COVID-19, SARS-CoV-2, Hyper inflammatory shock, Pediatric, Kawasaki disease.*

1. Introduction

MIS-C (Multisystem Inflammation Syndrome) or PIMS-TS (Pediatric Inflammatory Multiorgan Syndrome Temporally related to SARS-CoV-2); as a separate diagnosis; was first established in April 2020 [1]. Some of the affected children developed shock and multiorgan failure while others presented like Kawasaki or toxic shock [2]. The clinical evidence suggests that this inflammatory multisystem syndrome is temporally associated with severe acute respiratory syndrome corona virus 2. Like any new disease, uncertainties in prevalence, clinical phenotypes, severity, disease course, and best management are inevitable [3]. MIS-C incidence appears to be about 1 in 100,000 individuals <21 years old [4]. The definition depends on six criteria: childhood age group, persistent fever, high markers of acute inflammation, organ dysfunction, absence of alternative diagnosis, and relation with COVID-19 infection or exposure [5].

A child with persistent fever, inflammation (neutrophilia, increased C-reactive protein, and lymphopenia), evidence of single organ or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder) can be diagnosed as PIMS-TS according to the Royal College of Pediatrics and Child Health (RCPCH) definition after exclusion of any other microbial cause including bacterial sepsis and infections associated with myocarditis such as enterovirus. SARS-COV-2 PCR test can be positive or negative; some children may develop criteria for Kawasaki disease [6]. According to the CDC definition, an individual aged <21 years who has fever (≥38.0°C for ≥24 hours), with one or more of the following: (an elevated C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), elevated fibrinogen, elevated procalcitonin, elevated d-dimer, elevated ferritin, elevated lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin), and multisystem (≥2) organ clinical involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological);can be diagnosed as MIS-C if no alternative diagnosis can be found . He/She should also be positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or in contact with a COVID-19 case within the recent month [3]. The definition of sepsis in pediatrics is a systemic inflammatory response and organ or multiorgan dysfunction induced by infection. It seems that systemic inflammatory response and organ dysfunction are the two primary components of both sepsis and PIMS-Ts. A proof of infection or exposure to COVID19 to meet the case definition is not required according to The RCPCH criteria [5].

2. Clinical presentation

The typical presentation of PIMS-TS is a child with persistent fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions and, in severe cases, hypotension and shock. Headache, confusion, conjunctivitis, cervical lymphadenitis, cough, sore throat, hand and feet swelling, and syncope might be seen. All cases have a persistent fever of 38.5°C or more, clinical and laboratory findings of hyper inflammatory status and single or multiorgan dysfunction [6]. All have elevated laboratory markers of inflammation (e.g. CRP, ferritin), high to very high: neutrophils and D-dimer, with lymphopenia and hypoalbuminemia. Many patients also have elevated heart damage laboratory markers (e.g., troponin, B-type natriuretic peptide (BNP) or proBNP). Some patients develop myocarditis, cardiac dysfunction, and acute kidney injury [3]. 78% of cases have an indicator of SARS-Cov-2 recent infection PCR or IgG antibodies [6]. Some

patients needed fluids and oxygen to treat septic shock. In all cases, other microbial causes should be excluded. [6]. Differential diagnosis of PIMS-TS may include typical and atypical Kawasaki disease, toxic shock syndrome, sepsis, and macrophage activation syndrome [5].

3. Treatment

Any suspected case of MIS-C should be considered for hospital admission if there is any of the following findings: respiratory distress, abnormal neurologic findings or change in mental status, renal or hepatic injury, elevated inflammatory markers (CRP ≥10 mg/dl), abnormal ECG or BNP or troponin T [4].

Intravenous broad-spectrum antibiotics should be given in all cases according to the culture sensitivity tests and local microbial prevalence. Clindamycin should be added when toxic shock syndrome is suspected [6]. Multidisciplinary team should be involved early in any decision making regarding the following treatment options: supportive care, intravenous immunoglobulin, methylprednisolone, and biological therapies including IL-1 antagonists (Anakinra), IL-6 receptor blockers (Tocilizumab), and anti-TNF agents (Infliximab). Children with PIMS-TS may need evaluation by many specialists: (immunologist, infectious diseases specialist, pulmonologist, rheumatologist, cardiologist, intensivist, hematologist, pediatric surgeon, radiologist, and neurologist) [4]. High-dose steroids can be started without infection exclusion. When there is evidence of cardiac involvement (increased troponin, increased NT-proBNP, abnormal coronary arteries on echocardiogram or contrast-enhanced CT) the patient should be referred to pediatric intensive care unit (PICU) [2]. Afebrile children at least for 24 hours with stable cardiac function and otherwise well can be discharged from the hospital. They need to be followed up including echocardiography again in the first 1-2 weeks after discharge and have further follow-up six weeks later for all [2].

4. Case report

4.1 First Case presentation

A 12-year-old previously healthy girl has a high fever, abdominal pain, and diarrhea for five days. Yesterday, her abdominal pain worsened. She started to vomit almost everything by mouth with profuse watery diarrhea approximately 15 times in one day. Two weeks ago, she had cough and flu symptoms similar to the ones exhibited by her family at the time. On admission she was apathetic, hypotensive, and severely dehydrated. She received two 20 mL/kg boluses of normal saline, high flow oxygen, ceftriaxone, and metronidazole. Her White Blood Cells count: 5.07 k (Normal range 5-15k/µL), Elevated Neutrophils percentage to 81%. (Normal range 25-60%), low lymphocytes 12% (normal range 20-70%), Platelets: 282k (normal range 140-450k/µL). Her D. Dimer level was markedly high: 2.5 mg/L (normal range less than 0.5mg/L), with elevated CRP: 60 (normal range less than 5 mg/L), and high Ferritin: 151 (normal range 5-100 ng/ml). Her ALT was mildly elevated to 75 (normal Range 5-55 IU/L), and elevated Lactate: 1.89 (normal range 0.5-1.6 m mol /L), her kidney function was normal with Urea: 2.9 (normal range: 1.8-6mmol/L), creatinine: 46 (normal range: 17-43-µ mol/L). She also had mildly elevated B type Natriuretic Peptide BNP: 135 (normal rage less than 125 Pg. /mL). Her Urinalysis was normal, cultures of blood urine and stool were all negative.

SARS-Cov-2 IgG /IgM & PCR swab were negative, however her father swab 3 weeks ago was SARS-Cov-2 positive. Other viral PCR for respiratory viruses were negative. Abdominal ultrasonography was normal and her Echocardiography with Doppler in 2 different locations was unremarkable. Multidisciplinary team was involved early in the treatment as a case of PIMS-TS. This team included an infectious disease specialist, cardiologist, rheumatologist, and a pediatrician. The patient was given ceftriaxone, metronidazole for 3 days, methylprednisolone 2mg/kg for 2 weeks, enoxaparin 1mg/kg for 2 weeks, aspirin 5mg\kg for 6 weeks, and omeprazole 1mg\kg for 2 weeks, in addition to supportive treatments. She improved dramatically within three days. On day four, she had no diarrhea, vomit, nor fever, her blood test results improved dramatically and was subsequently discharged home. On the follow-up visit 2 weeks later, she was symptom-free with normal results in both laboratory and radiology investigations.

4.2 Second Case presentation

An 18-month-old baby girl, previously healthy, had two weeks of persistent fever, poor sleep, irritability, and anorexia. No other complains were there. Three weeks ago, she had a runny nose and cough like her sister; both attended the same daycare. Seven days later, she developed high persistent fever for two weeks without any response to oral Cefixime, oral ibuprofen or intramuscular ceftriaxone which was given as a treatment for upper respiratory infection in another outpatient clinic. In the emergency room, she was febrile, ill looking, and agitated. No rash, organomegaly, nor lymphadenopathy. No clear focus of infection was found. Her WBC was elevated at 12.300 (normal range 4-12 k/ µ L), neutrophils: 60% (normal range 25-60%), lymphocytes: 28 % (normal range 20-70%), platelets: 455,000 (normal range: 140-450k/ µL), elevated CRP: 73 (normal range less than 5mg/L),elevated ALT: 106 (normal Range 5-55 IU/L), Creatinine: 23 (normal range:17-43-µ mol /L), elevated Ferritin: 150 (normal range 5-100 ng/ml, very high D Dimer: 2 mg/l (normal range less than 0.5mg/l).BNP normal 123 pg./ml (normal range less than 125pg/ml). Her chest x-ray showed mild bilateral bronchial opacities. Urine analysis was normal. Abdominal ultrasound was also normal. Multidisciplinary team was involved early in her treatment including (intensive care specialist, cardiologist, rheumatologist, ID, and pediatrician).

Next day, D Dimer and ferritin increased to 3.6 and 160 respectively, with platelets increased to: 600,000/µL. Echocardiography demonstrated clear coronary arteries brightness, and mild Pericardial Effusion. SARS-Cov-2 IgG /IgM & PCR swab were all negative, however both parents are doctors working in a front-line hospital and none of them have had a positive swab. This baby was given a single dose of IVIG (2gr/kg) in a single session on day two post-admission, enoxaparin 1mg/kg/day subcutaneously for two weeks, aspirin 5mg\kg orally for six weeks, with ceftriaxone and vancomycin for 8 days. Fever recurred on day three post- admission and Methylprednisolone 2mg\kg was started and continued for seven days, then decreased to 1mg \kg\day for one additional week. By day 4 she was afebrile, her D-dimer decreased to 0.78, her CRP decreased to 14.3 and her ferritin decreased to 57 mg/L. She was afebrile for the rest of her admission and discharged at day seven. Two weeks later she was symptom free. Her recent echocardiography at day 30 was normal.

5. Discussion

Thirty-nine observational studies which included 662 patients showed that 71.0% of children (*n* = 470) were admitted to the intensive care unit, with 11 deaths (1.7%) reported. The average length of hospital stay was 7.9 ± 0.6 days. Fever (100%, *n* = 662), abdominal pain or diarrhea (73.7%, *n* = 488), and vomiting (68.3%, *n* = 452) were the most common clinical presentation. Serum inflammatory, coagulative, and cardiac markers were considerably abnormal. Mechanical ventilation and extracorporeal membrane oxygenation were necessary in 22.2% (*n* = 147) and 4.4% (*n* = 29) of patients, respectively. An abnormal echocardiograph was observed in 314 of 581 individuals (54.0%), with depressed ejection fraction (45.1%, *n* = 262 of 581) comprising the most common aberrancy. Aneurysms occurred in 47 patients (8·1%) (5).

It seems challenging to distinguish the child with a fever that needs investigations as a suspected case of PIMS-TS from other febrile children. In the meantime, children presenting with fever, abdominal pain, gastrointestinal, respiratory, or neurological symptoms who are stable and have no other clear cause for their symptoms should have the following initial blood tests done to help to identify whether they have PIMS-TS: full blood count, C-reactive protein, urea, creatinine, electrolytes and liver function (2). Then those with features that meet the criteria for PIMS-TS should have measurement of the following blood test: Blood gas and lactate, fibrinogen, ferritin, D-dimer, troponin, N-terminal pro-B-type natriuretic peptide, lactate dehydrogenase. These should be completed within 12 hours of admission to hospital.

1. SARS-CoV-2 RT-PCR test on an appropriate respiratory tract sample and SARS-CoV-2 serology.
2. Septic and viral screen (Lumbar puncture only if specifically indicated.)
3. 12-lead electrocardiogram
4. Chest radiograph
5. Echocardiogram.
6. In children with abdominal pain who meet the criteria for PIMS-TS and require imaging, an abdominal ultrasound scan should be the first-line investigation to rule out alternative diagnoses (e.g., appendicitis) (2).

First First-line therapy for all children is intravenous immunoglobulin at a dose of 2 g/kg, administered in a single or divided dose depending on the clinical picture and cardiac function (2). Second-line therapy is intravenous methylprednisolone (10-30 mg/kg), it should be considered as the next treatment option for children who remain unwell 24 hours after infusion of intravenous immunoglobulin, particularly if they have ongoing pyrexia. High-risk children include those younger than 12 months and those with coronary artery changes. These children should be given early intravenous methylprednisolone (10-30 mg/kg), alongside intravenous immunoglobulin) (2).

The third line option in children who do not respond to intravenous immunoglobulin and methylprednisolone is biological therapy; the decision to initiate this therapy should be made by a multidisciplinary team (3). Anakinra treatment appears safe in severe infections and in children with hyper inflammatory syndromes. In children with COVID-19 and hyper inflammation, Anakinra (>4 mg/kg/day IV or SC) should be considered for immunomodulatory therapy. Initiation of Anakinra before invasive mechanical ventilation may be beneficial (4).

Children with PIMS-TS who are SARS-CoV-2 positive on RT-PCR or antigen testing might be considered for antiviral therapy; Remdesivir is the first-choice antiviral therapy for SARS-CoV-2. Children older than 12 years should wear compression stockings (2).

Low-dose aspirin should be continued for a minimum of 6 weeks in all patients with PIMS-TS (2). When there are coronary artery changes by echocardiography with maximal z-score of 2.5–10.0 low-dose aspirin should be started; those with a z-score ≥10.0 should be treated with low-dose aspirin plus Enoxaparin or Warfarin (4). When thrombosis develops or an ejection fraction EF <35% present, then anticoagulation with Enoxaparin should be continued for at least two weeks after discharge (4).

6. Conclusion

The two reported clinical cases presented with similar findings to the ones reported in observational studies in the literature, additionally both patients showed significant improvement with the use of recommended first- and second-line drugs. Both patients were symptom-free at most recent follow up.

Children who have persistent fever associated with abdominal pain, diarrhea, vomiting, cough, neurologic symptoms should have primary blood tests to identify PIMS-TS: FBC: full blood count, CRP: C-reactive protein, BUN: blood urea nitrogen, Cr: creatinine, Electrolytes and liver function (2). Diagnosis of PIMS-TS can be made without confirmed Covid-2 infection. When a PIMS-TS case is suspected, then full investigations should be done as suggested above.

It is challenging to deal with parents of the affected child, especially when COVID tests are negative, however good explanation that PIMS-TS is still an evolving disease could be helpful. High BNP or pericardial effusion could be the only feature of cardiac involvement. Early multidisciplinary team approach seems mandatory from the very beginning, as the differential diagnosis of this disease with a handful of lethal cases could be difficult.

Despite the use of IVIG in the treatment of all diagnosed cases, steroids in regular doses could be a good alternative and need to be evaluated more. Optimal septic approach and aseptic precautions are recommended in all cases. Until now, isolation in negative pressure room is mandatory only when the infection is confirmed by the PCR swab or antigen. SARS-Cov-2 related medical impacts on children seems not well clarified yet. It seems necessary to develop molecular tests able to detect viral antigens that may cause such hyper inflammatory status. Regular updates about PIMS-TS should be mandatory.

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