

SARS-CoV-2-Related Multisystem Inflammatory Syndrome in an Immunocompromised Child with Osteosarcoma Revealed by Hepatocellular Failure

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Received: 10 May 2022; Accepted: 14 Jun 2022; Published: 20 Jun 2022

Citation: Ryouni K, Chahid I, Atrassi M. SARS-CoV-2-Related Multisystem Inflammatory Syndrome in an Immunocompromised Child with Osteosarcoma Revealed by Hepatocellular Failure. *Gastroint Hepatol Dig Dis.* 2022; 5(2): 1-4.

ABSTRACT

Introduction: Multisystem Inflammatory Syndrome in Children (MIS-C) is a new phenomenon reported worldwide with temporal association with COVID-19.

Objective: The aim of our case report is to clarify the manifestations of a pims syndrome in a osteosarcoma field, which can be confused with metastases.

Patients and methods: We report a case of a 12-year-old male patient followed for osteosarcoma of the right humerus who was admitted for hepatocellular failure with cutaneous-mucosal jaundice revealing a PIMS syndrome.

Results: The patient had initially received 3 courses of chemotherapy, followed by monobloc resection of the tumour mass and osteosynthesis, who met the case definition of PIMS-TS presented with fever, multi organ and mucocutaneous involvement, cardiovascular and gastrointestinal symptoms. His biological work-up showed a significant inflammatory syndrome with very high ferritin levels, high D-dimer and pro-BNP levels, associated with lymphopenia and liver cytolysis. An echocardiogram revealed a dilated cardiomyopathy with an LVEF of 13% associated with a moderate pericardial effusion. The work-up was completed by a PCR covid which came back negative, when the serology came back positive confirming a PIMS-TS. Therapeutically, he received a course of immunoglobulin, corticosteroid, and in view of the myocardial damage, he was put on Aspirin, ACE inhibitor, beta-blocker and spironolactone after normalization of his blood pressure. The evolution was spectacular, marked by a clear clinical improvement, the normalisation of biological parameters and the improvement of his LVEF on echocardiography.

Conclusion: Although the pathogenesis is not clearly known, immune-mediated injury has been implicated. We herein provide current information on this condition, in order to raise awareness amongst pediatricians.

Keywords

PIMS, COVID, Hepatocellular failure, Osteosarcoma.

Introduction

In many countries struggling with the burden of the coronavirus disease 2019 (COVID-19) pandemic, a distressing and unexpected

serious, delayed inflammatory syndrome has emerged among children and adolescents, a population previously thought to have been mostly spared by COVID-19. Pediatricians in the United Kingdom and elsewhere noted hospitalizations of children who developed fever and multisystem inflammation. Some of these children were critically ill with shock and multiorgan failure

and required intensive care and some had characteristics that were similar to Kawasaki disease (KD) or KD shock syndrome. The clinical evidence suggested the emergence of a pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PIMS-TS).

The Royal College of Paediatrics and Child Health (RCPCH) had announced the first definition of PIMS on 1 May [1]. Multisystem inflammatory syndrome in children (MIS-C) is an alternative name proposed in the United States of America (USA) [2] and adopted by the World Health Organization (WHO) [3]. Unlike PIMS, the MIS-C definition requires confirmed SARS-CoV-2 infection or COVID-19 exposure. PIMS-TS/MIS-C seems to be largely immune-mediated, triggered by COVID-19, with the induced hyperinflammatory syndrome possibly due to post-infectious cytokine storm, rather than a result of direct cell injury caused by the virus.

Observation

Here we report a case of a 12-year-old male patient followed for an osteosarcoma of the right humerus who initially received 3 courses of chemotherapy, but in view of the stationary aspect of the lesions, a monobloc resection of the tumour mass and an osteosynthesis were indicated, followed by 3 sessions of chemotherapy based on cisplatin and Adreamycin. Last treatment received 2 months ago. Currently in complete remission.

Currently admitted to the pediatric hepato-gastrology department 3 for a cutaneous-mucosal jaundice evolving for 10 days, associated with intense epigastralgia, post-prandial food vomiting and oedema of the lower limbs occurring in a context of apyrexia, asthenia and anorexia. He denied upper or lower respiratory tract symptoms, urinary symptoms, or skin rash. Although he denied any history of contact with SARS-CoV-2 and all family members were asymptomatic.

The clinical examination on admission found a very asthenic, generally altered and an icteric child. He had cyanosis of the lips and extremities, tachycardia at 143 bpm, CRT at 3 sec, blood pressure at 90/50mmHg, tachypneic at 28 cpm, correct saturation at 98% on free air, apyretic at 37.4°C, cold extremities with oedema of the lower limbs, soft, painless, taking the bucket, associated with facial edema, the urine dipstick was negative. Pleuropulmonary auscultation revealed a pericardial friction, without rales, abdominal palpation revealed a slight hepatic overflow without signs of jugular turgor. The day after his admission, a non-purulent conjunctivitis associated with cheilitis was noted. Neurologically, he presented hallucinations and tingling of the lower limbs. Given his history of osteoblastic sarcoma, a metastatic origin was suspected at first, leading to a thoraco-abdomino-pelevian CT scan that showed scattered bilateral ground-glass areas with a mosaic appearance of the pleuropulmonary parenchyma associated with a pleuropericardial effusion with cardiomegaly and anomaly of the left cardiac apex.

Laboratory analysis was remarkable for a hyponatremia at 116mEq/L and lymphopenia at 520, he had elevated CRP at 27mg/l, liver enzymes (ASAT at 362 and ALAT at 237UI/L), with hepatocellular insufficiency: TP at 37% and Fact V down at 33%. D-dimers was at 1, 75 mg/l, troponin at 0,093 ng/ml, proNT-BNP >2500 pg/ml, ferritin at 2794ng/ml and LDH at 710ui/l. Viral serologies (HVA, HVB, HVC, EBC, CMV AND HIV) have been performed and returned negative.

The child underwent an echocardiogram revealing dilated cardiomyopathy associated with a medium-sized pericardial effusion and a 13% LVEF. Due to the current context of the SARS cov 2 pandemic and the presence of lymphopenia, a disturbed inflammatory balance and the result of the thoraco-abdominopelevian CT scan, a nasopharyngeal covid PCR was requested and came back negative, but the SARS-COV2 IgG viral serology was found positive. Therapeutically, our patient received a course of immunoglobulin at a rate of 1g/kg/d, corticosteroid therapy at a rate of 2mg/kg/d, and in view of the myocardial damage, he was put on Aspirin 100mg/d, ACE inhibitor at 1.25mg/kg/d, beta-blocker and spironolactone after normalization of his blood pressure.

This therapy led to an improvement in clinical symptoms. His laboratory parameters normalized, with the exception of a mild hepatopathy. On follow-up, one month later, he showed a further decrease in liver enzymes, echocardiographic control showed LVEF increased from 30% to 13% at admission, and showed no clinical or laboratory signs of inflammation and had no subjective complaints. 4 months later, the evolution was marked by an improvement of the LVEF on echocardiography, back to 50% versus 13% with a very good clinical condition. He benefited from a bone graft to replace the osteosynthesis put in place after resection of his osteoblastoma.

Discussion

The impact of the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has been widespread. Initial reports worldwide showed that most children are asymptomatic or have mild or moderate disease [4,5]. However, there are now several reports of the pediatric multisystem inflammatory syndrome associated with COVID-19 (PIMS-TS) in children globally [6,7]. From mid-April to early May 2020, a cluster of children presenting to paediatric intensive care units (PICUs) in the UK with an unexplained multisystem inflammatory syndrome triggered an alert by NHS England and the UK Paediatric Intensive Care Society [8].

Children with this multisystem illness appeared to have overlapping features of Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome [9]. Since then, similar cases have been reported in the USA [10] and Europe [11], and received media coverage in the UK [12].

On May 1, 2020, the Royal College of Paediatrics and Child Health (RCPCH) published a case definition and guidance related to this multisystem illness [9], defining it as a persistent fever, inflammation, and evidence of single or multi-organ dysfunction in a child, with exclusion of any other microbial cause, with or without PCR evidence of SARS-CoV-2. In the UK, this condition has become known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), and in the USA, it has been defined as multisystem inflammatory syndrome in children (MIS-C), with a more restrictive case definition than that of PIMS-TS [10].

Our patient developed abdominal discomfort, systemic inflammatory response to SARS-CoV-2 infection in absence of other infectious pathogens. Unlike in some recently published patients [13], our patient did not fulfill diagnostic criteria for Kawasaki disease and instead displayed some but not all hallmarks of secondary MAS/HLH, fulfilling entirely the case definition criteria of PIMS-TS as proposed by both the Royal College of Pediatrics and Child Health and the Centers for Disease Control and Prevention (Table 1).

Hypothesised to be a post-infectious inflammatory response following SARS-CoV-2 infection, MIS-C appears to have distinct epidemiological and clinical features when compared to features of acute severe COVID-19 infection in children. Indeed, acute severe COVID-19 infection in children is associated with young age, a history of co-morbidity, respiratory symptoms and respiratory dysfunction [14] in contrast, the cases of MIS-C presented are older, did not frequently have co-morbidities, and the majority presented with gastrointestinal symptoms and significant cardiovascular dysfunction. These clinical features are similar to those recognised in the largest and most comprehensive MIS-C case series published to date (n = 99) [15].

Dufort et al. found that the majority of children diagnosed were aged between 6 and 12 years, 80% reported gastrointestinal symptoms, and 63% had cardiovascular compromise requiring inotropic support. A minority reported a cough (31%) or a comorbidity (31%). Our patient also met these criteria; he was 12 years old, had gastrointestinal manifestations without respiratory involvement and had significant cardiovascular failure. Despite its rarity, MIS-C is of significant concern due to the severity of

Table 1: Case Definitions for Emerging Inflammatory Condition During COVID-19 Pandemic from the World Health Organization, Royal College of Paediatrics and Child Health, and Centers for Disease Control and Prevention.

| World Health Organization | Royal College of Paediatrics and Child Health (United Kingdom) | Centers for Disease Control and Prevention (United States) |
|---|--|---|
| Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral non purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/ NT-pro BNP) 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (Diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, 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 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome | A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features This may include children fulfilling full or partial criteria for Kawasaki disease, Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative | An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection |
| Abbreviations: APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECHO, echocardiography; ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; PT: prothrombin time; RT-PCR: reverse transcriptase-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. | | a Criteria for Kawasaki disease include persistent fever and 4 of 5 principal clinical features: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash (maculopapular, diffuse erythroderma); erythema and edema of the hands and feet and/or periungual desquamation; and cervical lymphadenopathy. |

the illness, with the majority of children requiring intensive care treatment.

First-line therapy for all children is intravenous immunoglobulin at a dose of 2 g/kg, calculated using ideal bodyweight, which can be administered in a single or divided dose depending on the clinical picture and cardiac function. A second dose of intravenous immunoglobulin might be considered for children who have not responded or partially responded to the first dose.

Second-line therapy is intravenous methylprednisolone (10–30 mg/kg) and should be considered as the next treatment option for children who remain unwell 24 h 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). Gastric protection (eg, omeprazole) should be given to children on high dose steroids.

Biological therapy should be considered as a third-line option in children who do not respond to intravenous immunoglobulin and methylprednisolone; the decision to commence a biological therapy should be made by a multidisciplinary team. Our patient received 2 doses of immunoglobulin after a partial response to the 1st dose, associated with boluses of methylprednisolone, then relayed by oral corticosteroid therapy for 6 weeks, with a good clinical and biological evolution. 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

Intravenous antibiotics should be commenced in all patients; these should be focused or stopped based on the clinical picture and culture results. Children who meet the criteria for toxic shock syndrome should be given clindamycin in addition to broad-spectrum antibiotics. The initial infection screen does not have to be negative for other pathogens before commencing high-dose steroids.

The local Kawasaki disease guidelines for aspirin dosing should be followed for children with Kawasaki disease-like phenotype. Low-dose aspirin should be continued for a minimum of 6 weeks in all patients with PIMS-TS.

Conclusion

Despite the emerging literature, there are still a lot of unknowns regarding SARS-CoV-2. It is important to gather data on the condition to understand the damage caused and risk for recurrence as well as long-term implications including the risk for autoimmune disease later in life.

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