9-day high-grade spiking postoperative fever in a child with acute appendicitis: facing clinical systemic disorders in surgery setting

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Abstract

When dealing with a postoperative persistent fever in a surgical patient, multisystemic inflammatory disorders must be kept in mind, recognized at an early stage and suddenly managed multidisciplinary. We report about a life-threatening condition which was unlikely to be seen in a surgical context before the pandemic: the newly defined “Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 infection” (PIMS-TS) is suspected when a patient presents with consistent clinical features; In the 78% of patients, some COVID19 exposure can be documented. A paediatric case of hemophagocytic lymphohistiocytosis is reported (eventually falling into the PIMS entity), followed by a laparoscopic appendectomy for an acute gangrenous appendicitis. An alert to the community of pediatric surgeons is warranted, hopefully to be a hands-on update within the 2020 pandemic.

Introduction

We provide a controversial diagnostic case for debate and a brief “hands-on update” about the scenarios arising within this COVID pandemic that a surgeon may find himself to deal with. In fact, rare causes of persistent fever like multisystemic inflammatory disorders may eventually put a patient at risk of life-threatening complications if unrecognized at an early stage. Hemophagocytic lymphohistiocytosis (HLH) disorders involve defects in lymphocytes (leading to immune dysregulation, organ infiltration, and massive release of proinflammatory cytokines) and require a high index of suspicion to quickly start the therapy [1,2]. Clinical patterns range between signs and symptoms of sepsis, SIRS, shock and multi-organ failure [2]. Diagnosis is confirmed when at least 5 out of 8 criteria are met [3]: (1) fever; (2) Splenomegaly; (3) Cytopenias affecting 2 of 3 lineages in the peripheral blood: a) hemoglobin less than 90 g/L or less than 100 g/L in infants < 4 weeks; b) Platelets less than 100 x10⁹/L; c) Neutrophils less than 1.0 x 10⁹/L; (4) Hypertriglyceridemia and/or hypofibrinogenemia; (5) Hemophagocytosis in bone marrow, spleen or lymph nodes; (6) Low or absent NK-cell activity; (7) Ferritin greater than 500 ug/L; (8) Soluble IL-2 receptor (CD25) greater than 2400 U/mL. The treatment consists in a first step of trigger eradication (i.e., an underlying infectious agent) and then reducing the lymphocytes activation (steroids, etoposide, anti-T-cell agents, as well as new biologic treatments, and eventually allogenic stem cell transplantation). HLH can be primary (related to particular kinds of genes and immunodeficiencies), either secondary to infections (with the most common agent be the Epstein-Barr virus) or rheumatologic conditions (namely MAS: Macrophage Activation Syndrome). Other described potential triggers to be mentioned are medications, surgery, and during this last period, the COVID-19 agent [4-11]. In fact, the recently defined Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) is a life-threatening disease affecting children, likely related to some COVID-19 exposure and close resembling HLH and/or MAS [5-11]. Additionally, PIMS-TS may share some clinical features with Kawasaki disease, even the two entities distinctly differ. According to the proposed definitions, SARS-CoV-2 polymerase chain reaction (PCR) should be prescribed, regardless of the result of the serologic test, when a child presents signs of inflammation and organ dysfunction, and other causes of infection ruled out [8,9,11].

Case Report

On the 13th of May 2020 a 10-year-old girl was referred from a local hospital for primary care due to cervical lymphadenopathy, fever and abdominal pain at the right iliac fossa. Her past medical history highlighted a three-day fever and dry cough on the 31st of January, nonspecific but self-limiting abdominal pain over few days in February, a long-lasting oral aphthous ulcer, and a skin eyelid lesion in April, without conjunctival infection (Supplementary file 1). Since the 3rd May she experienced asthenia and fever along with severe sore throat and tonsillitis on the 9th. On the 10th, pharyngeal swab for SARS CoV2 was negative and the day after she presented at the Emergency Department of the local hospital for persistent fever and increased asthma. Blood tests
revealed a multisystem inflammation status with a positive pharyngeal swab for group A streptococcus (Table 1). A chest x-ray showed a hypo echogenic area in the right lower lobe. A Computerized Tomography Scan showed a suspected acute appendicitis: ascending retrocecal appendix of about 13 mm with signs of wall thickening and hyperemia, and a coprolite. Laparoscopic appendectomy at the same night revealed a gangrenous appendicitis. The postoperative stay was characterized by persistent, spiking, fever up to 40 °C (three to four peaks daily) and severe asthenia. Blood cultures resulted negative, but, in spite of good recovery from the abdominal intervention, laboratory work up still showed severe general inflammation. Intravenous systemic antibiotics were administered: cefotaxime (11th 14th May), clarithromycin (12th 14th May), metronidazole, gentamicin and ceftazidime (14th 16th May) and vancomycin and meropenem (16th 30th May). Cardiac ultrasound examination ruled out Kawasaki disease (16th and 21st May). Slit-lamp eye examination resulted negative. HLA typing was not informative for HLA B51 and B27. Considering the hypothesis of PIMS-TS, rectal swab and serologic tests for SARS CoV-2 have been performed, with negative results. On post-operative day 9, fever disappeared along with a gradual improvement of the laboratory tests (Table 1). The histopathology report of the retrieved specimen confirmed an acute appendicitis. The patient was discharged on the 1st of June and follow-up blood examinations on the 19th of June showed normal inflammation signs (Table 1).
Discussion

In dealing with persistent fever in a surgical patient, when other postoperative complications have already been ruled out, a high index of suspicion for systemic inflammatory disorders or complications is required to achieve a prompt diagnosis. As matter of fact, it has to be stressed that surgery can be a trigger for secondary HLH. Additionally, in this clinical setting, dealing with a such a patient in this "COVID Era"; SARS CoV-2 tests result mandatory in order to timely identify and properly treat PIMS-TS, as severe clinical entity, potentially leading to shock, myocardial dysfunction and eventually death.

Our patient experienced a high-grade persistent fever complicating the management of the postoperative course for nine days after a laparoscopic appendectomy. No alternative infectious as well rheumatic cause was identified, nor the appendicitis could explain by itself the severity of the general status of this otherwise healthy child. The antistreptolysin titers, not increased at further determinations, were not able to address Streptococcus as the underlying cause. Her laboratory tests matched laboratory criteria for HLH and/or MAS, including low levels of fibrinogen during persistent fever, and a drop of ESR over increasing value of CRP. Furthermore, she tested negative for SARS CoV-2 both at serology and PCR swab. No attributable close contact with a COVID patient was identified in the history, however consistent symptoms (fever and cough) were traced back to three months earlier.

While initial reports in the early pandemic era speculated about a COVID-related inflammatory syndrome must be raised. Multisystemic inflammatory disorders in general must be kept in mind when a persistent fever complicates a postoperative course and frequently require sudden and multidisciplinary management.

Disclosure Statement

None.

Authorship Contribution

S.U., G.S. and A.M. collected data; S.U., G.S. and A.M. analyzed data; G.V.R. gave technical support and conceptual advice; S.U. and A.M. wrote the manuscript; G.S., G.V.R. and R.C. participated in the final critically review process; A.M. and G.S. supervised the whole drafting process; All authors read and approved the final manuscript.

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