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Case Report

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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) 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), follo 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-threating 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 $x10^9$ /L; c) Neutrophils less than 1.0 x 10^9/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-threating 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, non-specific 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 injection (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 asthenia. Blood tests

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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).

Table 1. Laboratory Test results

	11/05	13/05	13/05	15/05	16/05	18/05	20/05	25/05	30/05	01/06	19/06
COVID-19 Nasopharyngeal swab	Negative										
COVID-19 rectal swab					Negative						
COVID-19 Serum IgM							Negative				
COVID-19 Serum IgG							Negative				
WCC (n/uL)	6360	4360	5840	4260	4660	6160	7580	6930	5600	5350	3810
Neutrophils (%)	66	73.2	78.6	72.5	69.8	61.6	60.8	54.1	42.7	33	24.6
Lymphocytes (%)			13.8	16.9	14.4	20.9	19.9	19.1	33.7	45.2	57.9
Eosinophils (%)			4.8	7	11.1	12.1	9.8	17.6	15.1	13.3	5.8
Hb (g/dL)		11.5	13.1	10.7	11.4	12.2	11	11.3	11.4	11.2	12.9
PLT (n/uL)		224	277	313	353	420	487	538	335	349	304
CRP (mg/dL)	4.36	7.24	10.3	5.76	5.37	3.46	1.45	0.77	<0.29	<0.29	<0.29
ESR (mm/h)		38	72	77	57	88	77	63	54	52	9
PCT (ng/ml)				23.7	14	4.5	0.9				
LAD (UI/L)	736	962	1218	935	1012	777	464	231			213
Fibrinogen Clauss (mg/dL)		416	544		386	540	520	502			
PT (%)		68	80		79	92	100	82			
aPTT (sec)		33	27		26	32	30	31			
INR (U)		1.32	1.16		1.17	1.06	1	1.14			
D-dimer (ug/L FEU)	7490	6980			>10000						
AT III (%)					103						
Ferritin (ng/ml)		2769	4577	5033	3584	1838	725	224			34
Colesterol (mg/dL)								149			
Triglicerid (mg/dL)		146	155	155	144	201	200	166			
Albumin (g/dL)			3.5					3.3			
Total protein (g/dL)		5.8	7.7		6.8	7.2	7				
Total Bilirubin (mg/dL)			0.7		0.5	0.5	0.4				
Direct Bilirubin (mg/dL)			0.3		0.2	0.1	0.1				
AST/GOT (UI/L)		109	156	156	149	102	43	24	32		19
ALT/GTP (UI/L)		74	111	112	128	127	84	43	45		19
gGT (UI/L)		63	124		294			96	65	57	21
CPK (UI/L)			58								
Creatinine (mg/dL)			0.55		0.53	0.4	0.47				
ASO (UI/ml)			355				338				
Ig Anti-DNAsi B (UI/ml)			486.7				454.8				
ANCA							Negative				
ANA							1.80				
ASCA							Negative				
Blood Culture			Negative	Negative							
Stool Culture						Negative					
Urine Culture	Negative										
EBV IgM	Negative	Negative									
EBV IgG	Negative	Negative									
EBV PCR (pharyngeal swab)				Negative							
EBV PCR (serum)			Negative	Negative							
EBV PCR (stool)					Negative						

CMV IgG (U/ml)	Negative	Negative									
CMV IgM (U/ml)	Negative	negative									
HSV IgM		Negative									
HSV IgG		negative									
Adenovirus PCR (pharyngeal swab)				Negative							
Adenovirus PCR (serum)			Negative								
Adenovirus PCR (stool)					Negative						
Rotavirus PCR (stool)					Negative						
Fusobacterium necrophorum PCR (swab)						Negative					
Bartonella Henselae Ab									Negative		
Listeria Monocytogenes Ab									Negative		
Yersinia enterocolitica/ Pseudotubercolosis Ab									Negative		
S.typhi antigen O and H Ab									Negative		
S.paratyphi C/B antigen O and H Ab									Negative		
Brucella sp Ab									Negative		
Toxoplasma IgM, IgG									Negative		

Abbreviations: PCT: Procalcitonin; PLT: Platelets; Hb: Haemoglobin; APTT: activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR: erythrocyte sedimentation rate; PT, prothrombin time; PCR: polymerase chain reaction; LAD: Lactic acid Dehydrogenase, ASO: Antistreptolysin O titer.

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. Even a proven evidence of SARS CoV-2 infection was not identified, clinical features and evolution of this patient may close represent PIMS-TS. However, although our patient did not require inotropic support or resuscitation and evidence of myocardial involvement was excluded, an integrated multidisciplinary management was necessary. On the other hand, previously reported cases of PIMS-TS where positive for PCR or IgG anti-body against SARS-CoV-2 only in 78% of children (n = 58) [10,11] and a prompt suspicion of this clinical entity should be maintained even a proved infection is not laboratory recognized.

Conclusion

While initial reports in the early pandemic era speculated about a minor involvement of the pediatric population, early warning about the 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

Declarations of Interest

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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