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(CASE REPORT)

Multisystem inflammatory syndrome and acute rheumatic fever coexisting in a child with prolonged fever

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Abstract

Fever is the most common and antique feature of disease especially in children. Although considered of benefit when is generated from infective causes, when it is prolonged or from non-infective origin it could be harmful. Here is reported the case of a nine-years old boy hospitalized for prolonged fever of unknown origin. A detailed examination revealed the co-existence of two immune mediated conditions in children, Multisystem Inflammatory Syndrome and acute Rheumatic Fever. A high index of suspicion should be maintained while evaluating a child for a systemic inflammatory disease due to COVID-19, it is imperative to consider other systemic disease of childhood or the coexistence of two disorders.

Keywords: Fever; Children; MIS-C; Acute Rheumatic Fever; Co-existence

1. Introduction

The normal human body temperature is considered to be 37 °C**,** but it varies approximately 1C in relation to several environmental and biological factors such as time of day, site of temperature measurements, level of physical activity, age, sex and race. The Infectious Diseases Society of America define fever as a core temperature of 38.3 °C or higher, i.e. just above the upper limit of a normal human temperature, irrespective the cause [1, 2].

Fever is known as a sign of disease since antiquity. It was first described by Celsius around 2000 year ago when he listed the four cardinal features of inflammation pain, heat, redness and swelling. Almost the same time Hippocrates discovered that fever was beneficious. Fever represents a complex adaptive response of the body to various immune challenges infectious or non-infectious one. The febrile response is a complex process due to multi-systemic effects generated by endocrine, neurological, immunological and behavioural mechanisms. Fever is not only a regulated rise in body temperature it is also accompanied by various sickness behaviours, changes in metabolic and physiological characteristics of body systems and alterations in immune responses [3]. The febrile response, plays a crucial role to the pathogenesis, clinical presentation and outcome of many illnesses and diseases. Despite its beneficial effects in promoting immune function and compromising bacterial and viral growth, when it exceeds in duration and degree it is accompanied by deleterious effects. A fever occurring in sepsis may be associated with a survival benefit, but this is not the case for non-infective triggers [4]. When heat generation exceeds heat loss, a combination of cellular, local, organ-specific and systemic effects occurs.

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Children experience higher and more prolonged fevers, more rapid temperature increases, and greater temperature fluctuations compared to adults, however a prolonged fever or fever of unknown origin is a very challenging one. Fever of Unknown Origin in adults was defined by Petersdorf and Besson in 1961 as a state of febrile illness for more than three weeks with a body temperature greater than 38.3˚C on several occasions and uncertain diagnosis after one week of study in hospital [5]. The definition of Fever of Unknown Origin in children varies from 1 - 3 weeks. Even with modern advances in medicine, it remains a challenge and may be a symptom of approximately 200 described cases. Classical Fever of Unknown origin is subdivided in four main etiological categories: infections, malignancies, non-infectious inflammatory diseases (NIID) and miscellaneous conditions. In children, infections lead the differential diagnosis followed by collagen vascular diseases, malignancy is typically not heralded by fever alone in childhood [6]. However fever will continue to be a cardinal manifestation of old, new and emerging diseases, whether infectious and non-infectious disease, therefore understanding fever and febrile response is vital in making the diagnosis, treatment and follow-up of various diseases.

This case report aims to highlights the potential causes of prolonged fever in children and the possibility of the existence of two different causes contemporary.

2. Case report

A 9 years old male B.D. admitted to the University Hospital Center of Tirana with a history of 2 weeks fever. He was treated with broad-spectrum oral antibiotics by a local clinic for but fever persisted in high values 39°C. All the family members were healthy and she had been healthy too till then. Vaccination was performed according to the age of the child. The family did not keep domestic animals at home and consumed safe food.

On physical examination the child appeared moderately ill, he high fever 39.5°C, nausea, abdominal pain, joint and muscle pain, fatigue. No stiff neck nor other neurological anomalies were observed. Sclera were slightly injected, and a slight pharyngeal injection too. No cervical lymphadenopathy, or edema were observed. A pseudo-urticarial, maculo-papular, non-pruritic, fade when blanching, non-stable rash was observed on lower extremities over the knees' and ankle' skin. Fig 1. There were found tachypnea with elevated respiratory rate of 35-40 breaths/min and fine rales on both fields in respiration, and tachycardia with elevated heart rate of 120 beats/min. The abdomen was soft, not distended, bowl sounds were present, liver and spleen were not enlarged on palpation.

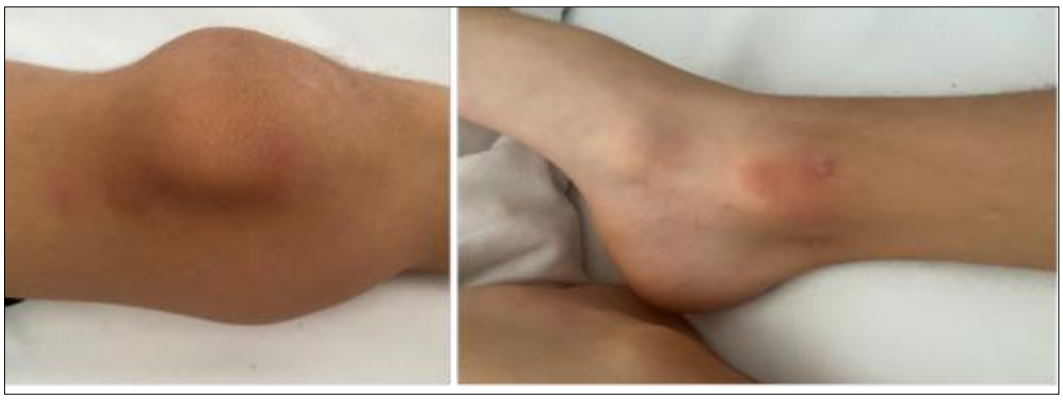

Figure 1 Skin Rash

Laboratory examination revealed : WBC 33,200 cells/mm^3 (25,600 neutrophils, 4,100 lymphocytes), RBC 3,670,000 cells/mm^3, Hemoglobin level 10.6g/dl, Hematocrit value 29.5%, Platelet count (PLT) 374,000 cells/mm^3, Erythrocyte sedimentation rate 41 mm/h (<15mm/h), Aspartate aminotransferase 48 U/L (21-44 U/L), Alanine aminotransferase 15 U/L (9-25U/L), blood Urea Nitrogen (BUN) 9.2 mg/dL (10.9-36 mg/dL), Creatinine 0.38 mg/dL (0.38-0.54 mg/dL), Lactate dehydrogenase enzyme (LDH) 235 U/L (192-321U/L), C reactive protein 9.06 mg/dL (<0.5 mg/dL), Fibrinogen activity 452 mg/dL (140- 360 mg/dL), Ferritin value 4770.64 ng/mL (13.7-79.8 ng/mL), Anti-streptolysin O (ASLO) 2135 IU/mL, C3 132.0 mg/dL, C4 21.1 mg/dL, RF <20.0 IU/mL (<30 IU/mL), ANA 160 (<160) [Tab.1].

Table 1 Laboratory values

WBC	33,200 cells/mm³ (4,000-11,000)
Neutrophils	25,600 cells/mm³ (1,280-6,490)
Lymphocytes	4,100 cells/mm³ (2,500-9,000)
RBC	3,670,000 cells/mm³ (4,000,000-5,300,000)
Hemoglobin	10.6g/dl (11-13 g/dl)
Hematocrit	29.5% (33-43%)
Platelet	374,000 cells/mm³ (150,000-400,000)
Erythrocyte sedimentation rate	41 mm/h (<15mm/h)
Aspartate aminotransferase	48 U/L (21-44 U/L)
Alanine aminotransferase	15 U/L (9-25U/L)
Blood Urea Nitrogen	9.2 mg/dL (10.9-36 mg/dL)
Creatinine	0.38 mg/dL (0.38-0.54 mg/dL)
Lactate dehydrogenase enzyme	235 U/L (192-321U/L)
C reactive protein	9.06 mg/dL (<0.5 mg/dL)
Fibrinogen	452 mg/dL (140- 360 mg/dL)
Ferritin	4770.64 ng/mL (13.7-79.8 ng/mL)
Anti-streptolysin O	2135 IU/mL (0-331 IU/mL)
C3	132.0 mg/dL (80-170 mg/dL)
C4	21.1 mg/dL (14-44 mg/dL)
RF	<20.0 IU/mL (<30 IU/mL)
ANA	160 (<160)

Radiologic examination of thorax and abdomen revealed peribronchial inflammatory changes. Abdominal ultrasound examination revealed slightly increased mesentery lymph-nodes and normal liver and spleen. Ultrasound examination of the heart revealed a mild mitral valve regurgitation v=2.4m/s. Serologic examination for Salmonellosis, Brucellosis, Rickettsiosis, HIV, EBV, CMV, and Mantoux test were negative. Cultures of throat, blood, urine and feces resulted in no bacterial growth. Serology for a recent infection of SARS-CoV-2 resulted positive for IgG anti SARS-CoV-2.

After the completion of all examination it was obvious that the child fulfilled the criteria for the diagnosis of MIS-C, based on the Centers for Disease Control case definition for MIS-C; fever, respiratory, cardiac, abdominal and joints affected, inflammatory parameters increased, evidence for recent SARS-CoV-2 infection with no other infectious cause [Tab.2]. Despite this the presence of rash, which was identified as erythema marginatum, mitral valve regurgitation, elevated streptococcal antibodies, joint pain, increased inflammatory markers fulfilled the criteria of Jones, 2 major and 3 minor for Acute Rheumatic Fever. After all the examinations it was obvious that MIC-C and acute Rheumatic Fever coexisted. The child was treated with broad spectrum antibiotics, prednisolone and aspirin. Although some improvement was observed in clinical signs and inflammatory markers, fever persisted and inflammatory parameters were increased too, in these conditions the decision to initiate IVIG as in Kawasaki disease was performed. After the competition of IVIG fever abated, blood parameters normalized and the child was feeling well [Tab.3].

Table 2 Centers for Disease Control case definition for MIS-C

(1) An individual aged < 21 years with:
(2) Clinical criteria: • A minimum 24-h history of subjective or objective fever≥38.0 ◦ C AND •Severe illness necessitating hospitalization AND •Two or more organ systems affected (i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological)
(3) Laboratory evidence of inflammation • One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin
(4) Laboratory or epidemiologic evidence of SARS-CoV-2 infection • Positive SARS-CoV-2 testing by RT-PCR, serology, or antigen OR • COVID-19 exposure within 4 weeks prior to onset of symptoms
(5) No alternative diagnosis
Abbreviations: CDC, Centers for Disease Control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

Table 3 Patient laboratory outcome

Day of treatment	**Day 1**	**Day 5**	**Day 10**
WBC	33,200 cells/mm^3	24,900 cells/mm^3	11,700 cells/mm^3
Neutrophils	25,600 cells/mm^3	17,100 cells/mm^3	7,400 cells/mm^3
C reactive protein	9.06 mg/dL	5.03 mg/dL	0.57 mg/dL
Ferritin	4770.64 ng/mL	2432.99 ng/mL	213.07 ng/mL
ASLO	2135 IU/mL	1357 IU/mL	648 IU/mL
Erythrocyte sedimentation rate	41 mm/h	91 mm/h	23 mm/h

3. Discussion

The general agreement is that fever is beneficial in infectious diseases, but this affirmation does not stand in fevers of non-infectious origin. So a child presented with prolonged fever is a great challenge to a pediatrician. The clinical approach in the presenting case, was focused on exploring the presence of an infectious diseases. This approach was comprehensive, as infectious diseases are the most common cause of prolonged fever worldwide, despite the geographic differences on the etiologic agent. Serology tests resulted negative for Brucellosis, Rickettsiosis, Enteric fever, Leishmaniosis, which are the most frequent causes of prolonged fever in children in Albania. Culture of blood, and urine samples, secretion of pharynx did not discovered any bacterial agent. Manthoux reaction test, serology for Epstein-Barr virus, Cytomegalovirus, HIV, and Toxoplasma were negative too.

Prominent increase of white blood cells, neutrophils and C reactive protein, which is an acute phase reactant, indicated enhanced inflammation. Ferritin, which is the cellular storage protein for iron and coordinates cellular defense against oxidative stress and inflammation, is also an acute-phase reactant. Highly increased level of ferritin is an indicator of enhanced inflammation too. Facing these laboratory evidence, attention was driven towards non-infectious inflammatory conditions of childhood.

After COVID-19 outbreak in 2020, a novel inflammatory condition was added to the diapason of non-infectious inflammatory disorders of childhood. Designated as multisystem Inflammatory Condition associated with COVID-19 in children (MIS-C), it was firstly described in May 2020 in several highly endemic countries. It developed after the infection rather than during the acute stage of COVID-19, with clinical features both similar and different from other

well-known inflammatory syndromes in children such as Kawasaki disease, Kawasaki disease shock syndrome and toxic shock syndrome [7, 8]. The proposed case definition from the Centers for Disease Control and Prevention included fever, elevated inflammatory markers, and organ dysfunction not attributed to another infectious cause [Tab.2]. The majority of children were previously healthy and the most affected were children between six to 12 years old. Children with MIS-C presented with consistent cellular activation affecting multiple hematopoietic lineages. Almost all studies of MIS-C have identified high levels of inflammatory cytokines INF-α, INF-ɣ, INF-1β, IL-6, IL-8, IL-10, IL-17 [9, 10]. NK cells also show evidence of increased activation with higher expression of enzymes and T cells were elevated in number too. This multi-lineage immune activation is implicated in enhanced tissue inflammation with multi-organ function compromise [11, 12]. The serologic findings of MIS-C reflect the post-infectious stage of the disease. Higher levels of total and neutralizing antibodies against the spike protein have been present in children with MIS-C than in those with acute infection. Furthermore children with MIS-C have higher antibodies against other common viruses as common coronaviruses, influenza, respiratory syncytial, Epstein-Barr virus [13]. Increased levels of circulating autoantibodies have been identified including antigens in endothelial cells and gastro-intestinal tract, those associated with rheumatologic disorders and those of widely expressed tissue antigens. On May 2023, the COVID-19 public health emergency ended however, COVID-19 continues to be a health risk. The presenting child fulfilled all the criteria features of the approved case definition of MIS-C: fever, past COVID-19 infection confirmed by serology, elevated inflammatory markers, more than two organ-systems affected (pulmonary, gastro-intestinal, muscle-skeletal), no other infectious cause.

Although the consequences of COVID-19 global pandemic including MIS-C are still a fresh memory, and as a first impulse the medical attention is drown towards them, other systemic diseases have settled their role long ago. Acute rheumatic fever was first described in 1950 and continue to inflict a great burden in public health globally. Its incidence is estimated to be 8-51 per 100,000 people throughout the world, and children aged 5-15 years are most commonly affected [14, 15]. The incidence of Acute Rheumatic Fever in Albania is significantly decreased in the recent years due to increased socio-economic status and due to vast use of antibiotics in children. Acute rheumatic fever is a systemic illness that may occur following group A beta hemolytic streptococcal pharyngitis in children. It affects the heart, joins, skin, central nervous system, abdomen, and is believed to result from an autoimmune response; most authors have proposed that molecular mimicry between streptococcal and human proteins which involves both the B and T cells of peripheral blood, with infiltration of the heart by T cells is the inflicted immune mechanism. Others believe that an increased production of inflammatory cytokines is the final mechanism of the autoimmune reaction that causes damage to cardiac tissue [16, 17, 18].

The highly increased blood level of anti-streptolysin O and the negative throat culture in the presenting child indicated a previous group A streptococcal infection. Skin involvement with pseudo urticarial rash around the knees and ankles which were blanching, non-pruritic and unstable, indicated erythema marginatum, and together with the mild regurgitation flux in the mitral valve composed two major criteria of Jones. Fever, myalgia, leukocytosis, increased erythrocyte sedimentation rate and C reactive protein fulfilled the minor criteria of Jones. The diagnosis of Acute Rheumatic Fever was performed. Obviously the child suffered from two multisystem autoimmune inflammatory diseases contemporary. This coexistence inflicted an enhanced inflammatory response with highly increased neutrophils count, highly increased erythrocyte sedimentation and also highly increased acute phase reactants as C reactive protein, ferritin and prolonged fever.

4. Conclusion

Prolonged fevers are very challenging in children. COVID-19 global pandemic came with a new inflammatory disorder in children, known as MIS-C. A high index of suspicion should be maintained while evaluating a child for a systemic inflammatory disease due to COVID-19, it is imperative to consider other systemic disease of childhood or the coexistence of two disorders.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors declare no conflict of interest.

Statement of informed consent

Informed Consent was taken from the parents of hospitalized child included in the study, for using the data of their medical records, providing anonymity.

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