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Case Report

A Rash Diagnosis in the Post-Pandemic Era

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Abstract

The clinical case of a young girl admitted to a District General Hospital is summarized to highlight an important cause of fever and rash in pediatrics. Researchers have included the clinical features along with three images highlighting progression of disease and five MCQs to demonstrate clinical reasoning and to affirm learning points after managing the case. The case occurred during the COVID-19 pandemic and increasing incidence of PIMS-TS, but emphasizes the importance of a broad thought process, despite the increasing incidence of newer conditions in children. Researchers have provided discussion to stress the similarities between conditions and to encourage pediatricians to keep a wide differential when considering causes of fever and rash in children. Researchers provide interesting reading and encourage independent thought on this serious but thankfully rare condition.

Keywords: Pediatrics; Dermatology; Fever; COVID-19; Rash.

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Introduction

Researchers discuss the case of a 10-year-old girl presenting to a District General Hospital with signs of a multisystem inflammatory condition during the SARS-CoV-2 COVID-19 pandemic, with focus on local management.

Summarizing clinical details, researchers include three photos (with consent) and five multiple choice questions to highlight similarities and differences in the plethora of multisystem conditions affecting children. Answers to each MCQ are used to form discussion around each condition, and authors welcome correspondence on the topic moving forward. This was and is particularly topical given the increasing incidence of PIMS-TS related to COVID-19 but serves as a reminder to maintain a broad differential as general pediatricians, despite the emergence of newly recognized

conditions, and to refrain from making a rash or hurried diagnosis no matter how prevalent any particular condition may be at the time.

Case

A 10-year-old girl presented to a District General Hospital with a 5-day history of fever, abdominal pain and sore throat with new onset conjunctivitis, the latter prompting presentation. On examination patient had hyperemic lips, an erythematous injected pharynx with a few buccal blisters, cervical lymphadenopathy and a faint maculopapular rash to trunk and palms. The conjunctiva was injected bilaterally. There was no meningism or neck stiffness. Patient was hemodynamically stable and had a temperature of 37.9˚C.

The patient had been commenced on oral Aciclovir by the GP prior to presentation and the fever was no longer responsive to Paracetamol and Ibuprofen used at home. Patient was born in the UK and fully vaccinated. An intravenous cannula was sited, and initial investigations showed mildly elevated C-reactive protein (44.8mg/L) lymphopenia (lymphocytes 1.1 × 10^9/L), and thrombocytopenia (134 × 10^9/L). A peripheral blood culture and conjunctival swabs were taken. Urine revealed 100 mg/dL proteinuria, chest X-ray was unremarkable. COVID-19 nose/throat swab PCR was negative.

Question 1

Which of the following differential diagnoses is LEAST likely?

A. Kawasaki disease
B. Toxic Shock Syndrome (TSS)
C. Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)
D. Paediatric Multisystem Inflammatory Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS)
E. Measles

Case (cont.)

Patient was commenced on intravenous Ceftriaxone and maintenance fluids due to reduced oral intake. Oral aciclovir and regular antipyretics were continued. Over the next 5 hours patient had unrelenting fever and widespread progression of the maculopapular rash with fissuring and scabbing of the lips (Figure 1).

Further tests were sent including D-Dimer, fibrinogen, ferritin, lactate dehydrogenase and markers of cardiac dysfunction (Troponin-T, brain natriuretic peptide). SARS-CoV-2 serology and stool PCR were added, and a serum-save sample sent.

Question 2

Which treatment would you add next in view of patient clinical progression?

A. Intravenous Immunoglobulin (IVIG) 2gram/Kg
B. Aspirin 7.5-12.5mg/kg four times a day until afebrile
C. Intravenous clindamycin 10mg/kg four times a day
D. All of the above

Case (cont.)

Fever persisted for a short period after the IVIG was completed and patient became afebrile 2 hours after the above listed

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medications were commenced. Following this, the conjunctiva became severely chemotic with hyperemia and blood-stained tears. The skin on the cheek began to superficially exfoliate in response to light touch (Figure 1).

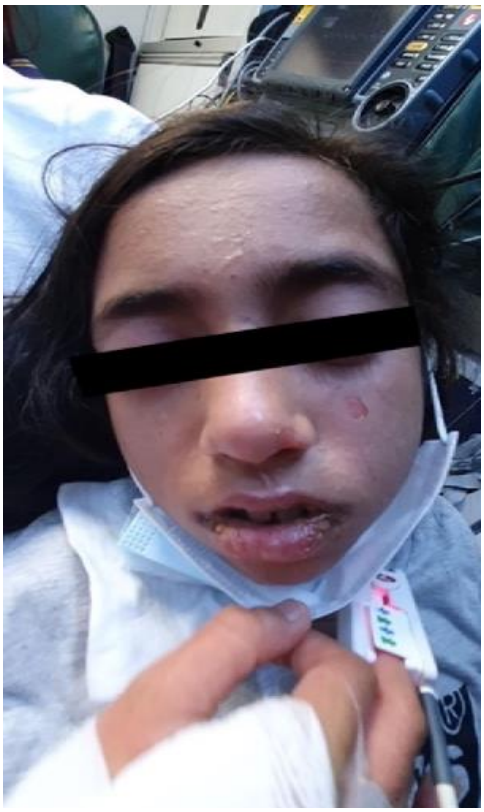

Figure 1: Facial appearance including lip cracking and superficial exfoliation of cheek.

Question 3

What is the name of the dermatological sign described on the patient's cheek and seen in Figure 1?

A. Koebner phenomenon
B. Nikolsky's sign
C. Asboe-Hansen sign
D. Koplik spots

Case (cont.)

Investigations revealed mildly elevated D-dimer, progressive anemia (Hemoglobin 108g/L), lymphopenia (0.9 × 10^9/L), hyponatremia (129mmol/L) and thrombocytopenia (platelets 128 × 10^9/L). Markers of cardiac dysfunction (Troponin T and brain natriuretic peptide) were normal. Bedside echocardiography demonstrated normal cardiac structure and function with normally sized coronary arteries.

The widespread maculopapular rash became purpuric and hyperpigmented, and small vesicles appeared at the margins of nails and nipples. Patient developed superficial bullae at pressure areas which became larger and ruptured, followed by desquamation of large patches (seen in Figure 2 and 3). Blood cultures showed no bacterial growth. Patient blood pressure remained stable.

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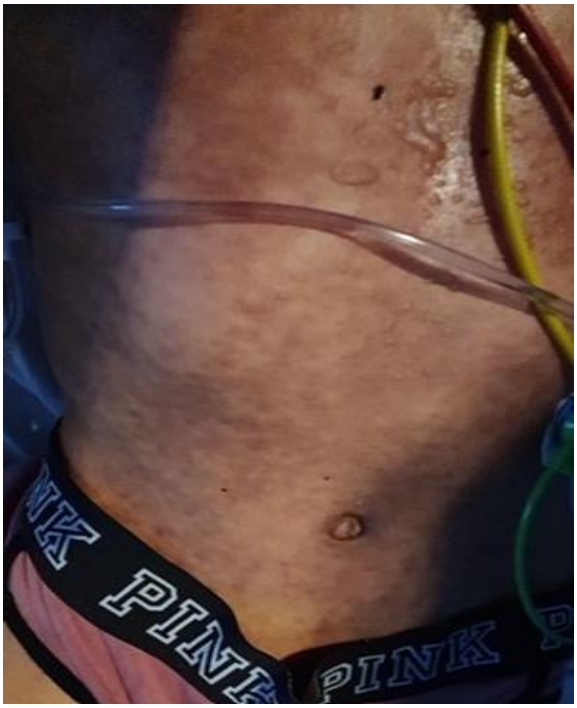

Figure 2: Trunk, depicting further superficial desquamation.

Figure 3: Widespread maculopapular rash and superficial bullae.

Question 4

In consideration of the progression above, which of the following is the most likely diagnosis?

A. Kawasaki disease
B. Toxic Shock Syndrome (TSS)
C. Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)
D. Paediatric Multisystem Inflammatory Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS)

Question 5

Of the treatments mentioned in the case, which is the most likely underlying cause?

A. Paracetamol
B. Ibuprofen
C. Ceftriaxone
D. Clindamycin
E. Aciclovir

Answers

Question 1: Answer E

All the options listed would be reasonable differentials in any case of persistent fever for 5 days. However, an immunocompetent child having received the MMR vaccination would not normally suffer severe measles infection. Whilst conjunctivitis is a feature of measles, there was no cough or coryza and one expects a morbilliform rash that usually descends from the hairline [1]. Most cases of Kawasaki disease affect under 5s [2], but it can occur in older children. With increasing infection rates of COVID-19, PIMS-TS (MIS-C in USA) is becoming more common in the UK and presents with similar clinical features to Kawasaki disease, TSS and the spectrum of SJS/TEN [3]-which at this stage of the case are poorly distinguishable without further investigation. A negative SARS-CoV-2 PCR does not rule out a diagnosis of PIMS-TS.

Question 2: Answer D

Despite the clinical progression and initial investigations, the differential remains wide, and there is no resolution of the fever, potentially all the above would be used in discussion with tertiary infectious disease teams. It would be advisable to add Clindamycin to Cephalosporin use due to its activity against anaerobic bacteria and reduction of Staphylococcal and Streptococcal toxin production [4,5]. High dose IVIG is used as immunomodulation in difficult to treat bacterial and viral infections [6] and is indicated for use in Kawasaki syndrome when diagnosed by a pediatrician or immunologist, in TSS with isolation of causative organism, and in SJS/TEN when diagnosed by a dermatologist and involving more than 10% TBSA [7]. It is now also recommended in the treatment of PIMS-TS in the UK [8]. When suspecting Kawasaki disease, it is advisable to use Aspirin until it is confirmed that coronary artery aneurysms have not occurred, although should be used with caution in bleeding or thrombocytopenic patients. In Kawasaki, Aspirin is given initially as high dose until defervescence and then reduced to 3-5mg/kg once a day and discontinued at 6-8 weeks once echocardiogram normal. It is important to save serum before the use of IVIG, in case the patient's antibody status needs to be determined at a later date, as SARS-CoV-2 antibody testing is being increasingly used in diagnosis of PIMS-TS.

Question 3: Answer B

Nikolsky's sign refers to desquamation of the most superficial layer of skin secondary to tangential pressure over a bony prominence, and is pathognomonic for pemphigus, SJS/TEN and Staphylococcal scalded skin syndrome [9]. Asboe-Hansen sign refers to the enlargement of a bulla on application of direct pressure in pemphigus and bullous pemphigoid. Koebner phenomenon is the appearance of new lesions of an existing dermatosis in areas of trauma in otherwise healthy skin and occurs in vitiligo and

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psoriasis [10]. Koplik spots are tiny white lesions seen inside the mouth in measles.

Question 4: Answer C

Although there is much clinical overlap between the options presented, case features are most suggestive of SJS/TEN. These conditions exist along a spectrum (TEN being more severe) involving sheet-like skin loss almost exclusively precipitated by medication. Pharyngitis, abdominal pain and conjunctivitis along with development of vesicles, bullae and purpuric macules over time are all clinical features of this condition. Anemia and lymphopenia are extremely common (>90%) [11], and proteinuria can occur. Hemodynamic stability, mildly elevated CRP and negative blood cultures make TSS less likely. Widespread desquamation and purpuric papules are not typical of Kawasaki disease nor PIMS-TS. Note that absence of early coronary artery aneurysms on echocardiography does not rule out Kawasaki disease. Although the incidence of SJS/TEN is rare in children this spectrum presents with a high mortality.

Question 5: Answer B

Although most of the medications listed can cause SJS/TEN, the clinical process began before presentation to hospital. Of the medications included in the case; non-steroidal anti-inflammatories (NSAIDs), Cephalosporins and Paracetamol are all recognized to cause SJS/TEN, as well as most Anticonvulsants, Sulfonamides, Penicillin and Allopurinol. In children, retrospective studies have identified 72-90% of cases of SJS/TENS are caused by a drug reaction [12]. It is most commonly the -oxicam variants of NSAIDS that trigger TEN, Ibuprofen was thought to be the most likely culprit in this scenario based on its use prior to presentation. ALDEN, an algorithm derived from use in adults, can be a useful tool to facilitate the identification of potential culprit drugs in SJS/TEN [13].

Patient outcome

The desquamation developed to involve 60% total body surface area, requiring biosynthetic skin dressings and transfer to a burns specific pediatric intensive care unit for supportive care. The patient was ventilated for close to 4 weeks. After a month in hospital, patient made a good recovery and was discharged. On last follow-up patient was well with no scarring of skin, instead areas of residual hyperpigmentation, which were fading. The patient is under ophthalmological follow up for corneal ulceration and is avoiding Ibuprofen for the time being.

SJS/TEN

SJS/TEN are immune mediated clinical diagnoses which need detailed systemic history taking and thorough examination and require subsequent multidisciplinary involvement in the supportive care and management.

TEN is extremely rare in children with an incidence of 0.4-0.5 cases per million per year with a lower mortality in children compared to adults [13]. Recurrence of SJS/TEN is more common in children compared to adults which may be due to recurring infections that are causal and precipitate this response [13]. Along the SJS/TEN spectrum, differentiation can be made through calculating the percentage of body surface area affected as shown in Table 1 (below) adapted from

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SJS/TEN: Where are we now? Ramien M, Goldman JL [12]. This is important as TEN is associated with longer duration of hospital stay and higher mortality [14]. The criteria have been adapted from adult studies but does not define those patients with severe mucosal involvement but minimal to no skin lesions [12].

	SJS	SJS/TEN	TEN
Body Surface Area Affected (BSA)-blistered, erythematous skin that is detachable	<10%	10-30%	>30%

Table 1. Spectrum of SJS/TEN, adapted from SJS/TEN: Where are we now? Ramien M, Goldman JL [12].

The Score of Toxic Epidermal Necrolysis (SCORTEN) is a predictor of prognosis for TEN that is widely used in adults. It involves adding up points for each prognostic factor which includes involvement of BSA, tachycardia and biochemical markers such as serum glucose, serum bicarbonate and serum urea [15]. More recently it has been trialed in a retrospective review and found to be a useful predictor of morbidity in the pediatric population [15].

Conclusion

Researchers felt it important to highlight this case in the current climate to emphasize that whilst the incidence of PIMS-TS is increasing during the pandemic era, one must keep a wide differential and not neglect important pathology causing systemic symptoms such as rash. Researchers present a summary of local learning points on this case, and welcome discussion on this topic.

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