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Severe cutaneous manifestations in a child with refractory Kawasaki disease

Sir, We report a child with refractory Kawasaki disease (KD), who presented severe scattered crusting skin lesions as predominant manifestation of the disease.

Case report

A 17-month-old boy presented to our department with a 3 day history of fever reaching 39°C, resistant to amoxicillin, along with a maculopapular rash on the face, trunk and limbs. Past medical history was unremarkable. Routine laboratory work-up revealed erythrocyte sedimentation rate (ESR) 72 mm/h, C-reactive protein (CRP) 13.67 mg/dl (nv < 0.35), haemoglobin 10 g/dl, white blood cell count 26,50 x 10^3/mm^3, fibrinogen 837 mg/dl and sodium 129 mEq/l (Table 1). Microbiological evaluation for bacterial and viral infections, including adenovirus, cytomegalovirus, parvovirus, herpes and Epstein–Barr virus, Staphylococcus and Group A Streptococcus, were negative. Throat, nasopharyngeal and cutaneous swabs for culture were also negative. Chest X-ray and abdominal ultrasound were unremarkable. On the day after admission, he developed non-exudative conjunctivitis, cervical lymphoadenopathy and mucusitis, and KD was suspected. Echocardiogram revealed normal systolic and diastolic left ventricular dimensions (29/19 mm), with normal fractional shortnening (32%) and ejection fraction (56%). The diameter of the left coronary artery was increased: 3.6 mm (z-score size for age: 2.5 mm). Intravenous immunoglobulin (IVIG) and aspirin were promptly administered on day 5 from the fever onset. Notwithstanding, fever rose up to 40°C and a significant worsening of the skin lesion occurred: itching and burning tender rash all over the body, scalp included. Cracked and scabbed lips appeared. A further IVIG cycle resulted unsuccessful in subsiding fever and cutaneous manifestations that later also presented blisters at the ankles and ear lobes. The ESR and CRP were still raised and platelet count rose up to 771 x 10^3/mm^3.

On day 8, an echocardiogram confirmed the previously reported coronary lesion. Despite a third dose of IVIG on day 10, fever persisted and diffuse scabs progressively involving cheeks, forehead, eyelids and legs occurred (Fig. 1). Intravenous methylprednisolone (MP), 30 mg/kg, was then given on day 11, but two additional steroid pulses were required over the following days, due to the persistent spiking fever along with elevated inflammatory parameters. On day 16, fever dropped and skin alterations significantly improved. Peeling at fingers and toes was then noted. No changes were detected on echocardiogram and the boy was discharged on aspirin (3 mg/kg). At 1 month follow-up, he had complete resolution of skin lesions and echocardiogram showed normal coronary artery diameter. Artery peripheral involvement was excluded by systemic echo Doppler evaluation.

Table 1. Laboratory values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 3</th>
<th>Day 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>72</td>
<td>56</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>13.67</td>
<td>0.31</td>
</tr>
<tr>
<td>White cells (per mm^3)</td>
<td>5100</td>
<td>12.540</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Platelets (per mm^3)</td>
<td>300.000</td>
<td>1.057.000</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>10</td>
<td>8.5</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>129</td>
<td>138</td>
</tr>
<tr>
<td>Albumin (%)</td>
<td>48.6</td>
<td>34.6</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>837</td>
<td>732</td>
</tr>
<tr>
<td>C5 (90–180)</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td>C4 (10–40)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
<td>762</td>
<td></td>
</tr>
<tr>
<td>IgA (UI/ml)</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>IgM (mg/dl)</td>
<td>112</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. (A) A 17-month-old boy with the Kawasaki disease: extensive cutaneous crusts all over the body. (B) Echocardiographic finding of dilatation of the left coronary artery.
The authors have declared no conflicts of interest.

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Discussion

Our patient’s case is interesting since the skin involvement predominated the other manifestations of KD through the course of the disease. In addition, he was resistant to current therapeutic regimen.

An erythematous rash, usually appearing during the acute phase, is part of KD diagnostic criteria. Commonly transient, possibly missed, it may also last 1 week or more. It is reported as non-pruritic, non-vesicular, non-bullous and non-crusting, but possibly purpuric [1, 2]. However, the occurrence of a pustulo-vesicular skin eruption in KD has been recently reported in a 4-yr-old boy [3].

In our case, the rash was typically maculopapular at admission, but over time, it became burning, itching and then vesicular-like and crusting. This eruption suggested Steven-Johnson syndrome as a possible diagnosis, but, in our case, the clear sparing of oral and anal orifices was in contrast. Otherwise, laboratory evidences for considering an infectious disease were also lacking. Persistent spiking fever, conjunctivitis, cervical lymphadenopathy and micositis along with coronary artery dilatation prompted us to introduce appropriate therapy for KD. However, fever and skin lesions subsided just after three IVIG and three MP pulses, sequentially administered.

To reduce the rate of coronary involvement, current clinical guidelines claim prompt IVIG administration in case definition suggestive for KD, even if the criteria are not fulfilled, mostly in the presence of coronary lesions [1, 2]. Despite timely introduction of IVIG, 10–15% of the patients do not respond [4–7], and, due to the high risk of coronary sequelae related to long-lasting fever, alternative therapy are considered [1, 2].

Guidelines for refractory patients are still lacking and different regimens have been proposed. An additional 2 g/kg of IVIG therapy is successful in all the patients fail to respond to the first infusion, but 4% of them fails to defervesce as well, and either a third IVIG cycle or corticosteroids are recommended [4–9]. In our patient, a third IVIG cycle was unsuccessful and three successive MP pulses were required to obtain a sustained resolution of fever along with skin recovery.

Timing and use of steroid therapy is still under debate in KD, but it should be considered if there is no response to two or three previous standard doses of IVIG [7–9].

Several anecdotal case series as well as small cohort report successful results of cyclophosphamide, ciclosporin, ulinastatin and infliximab for KD patients resistant to IVIG and corticosteroid regimes [1, 2, 10]. The experience is still anecdotal and no firm conclusions may be drawn before controlled trials are available.

In our patient, since the signs and symptoms of the disease subsided with the last MP pulse, and coronary artery lesions completely disappeared, the decision for an immunosuppressant/biologic drug use was referred and further considered no more.


Is TNFα really a good therapeutic target in motoneuronal degeneration? A case of amyotrophic lateral sclerosis in a patient with RA receiving infliximab

Sir, Tumour necrosis factor-α (TNF-α) has been implicated in the pathogenesis of various inflammatory conditions such as rheumatoid arthritis (RA), Crohn’s disease and psoriasis. In these diseases, TNF-α blockade is a successful and safe treatment option [1]. TNF-α can be neurotoxic and has also been implicated in the pathogenesis of some central nervous system diseases where inflammation has recently emerged as a significant contributor to motor neuron damage [2]. TNF-α acts as the main driver for neuroinflammation in amyotrophic lateral sclerosis (ALS). Animal studies [3–5] as well as phase II clinical trials are currently underway to test the validity of TNF-α as a drug target in ALS [6].

Four cases of concomitant RA and ALS have been reported to date [7, 8] but the occurrence of the two diseases in the same patient is probably due to chance alone. Here we report a case of an RA patient who was diagnosed with ALS while receiving the anti-TNF-α agent infliximab. ALS was rapidly progressive despite infliximab therapy.

An Asian man with non-insulin-dependent diabetes mellitus, hypertension, ischaemic heart disease and a permanent pacemaker was first seen in 1998 at the age of 68. He had a 9-month history of progressive symmetrical polyarthritis involving the hands, wrists, shoulders, knees, ankles and feet with morning stiffness. A diagnosis of seropositive erosive RA was made and treatment with methotrexate (MTX) was started. However, he still required concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and steroids. Sulphasalazine was added to his treatment without significant improvement. In August 2001, his disease remained active with a DAS28 score of 5.2. Treatment with infliximab...