A Case of Complete Adult-Onset Kawasaki Disease: A Review of Pathogenesis and Classification

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Abstract
Kawasaki disease (KD) is an acute systemic vasculitis that occurs primarily in children and rarely in adults, possibly after bacterial or viral infections in genetically susceptible hosts. KD may frequently be undiagnosed especially in adult patients without the presence of all the classical clinical criteria (incomplete or atypical KD). In addition, many differential diagnoses could be considered. Here, we report a case of KD in an adult patient with clinical features characteristic of the classical form. KD requires a long-term management in both paediatric and adult patients, in order to avoid complications that could follow both the acute and retrospective diagnoses of KD.

Introduction
Kawasaki disease (KD) is an acute systemic vasculitis that occurs primarily in children and rarely in adults [1]. It is defined 'complete' when the diagnosis is based on the presence of at least 5 days of fever and 4 of the 5 principal clinical features, in particular polymorphous exanthema or changes on the extremities such as erythema and oedema of the hands and feet, with subsequent desquamation of the fingers and toes [2]. Conversely, when not all the clinical criteria are fulfilled, KD can be defined as 'incomplete'. Other authors use the term 'atypical' KD to describe cases with atypical symptoms that are not common in classical KD, such as renal impairment, acute surgical abdomen and pleural effusion [2]. We present the case of an adult-onset KD which fulfilled all the criteria of 'complete' KD. Furthermore, we analyse the classification of the disease in adult patients.

Case Report
A 21-year-old male Caucasian patient was referred to the emergency department for atypical acute exanthema initially interpreted as allergic eruption. On admission, the patient was febrile (39.0°C) and complained of chills. Chest X-ray and electrocardiogram alterations were normal. The patient was febrile for 4 days and was initially treated with systemic antibiotics (amoxicillin-clavulanic acid 1 g twice daily) without benefits. The patient was then hospitalized, and a dermatologist’s evaluation was requested. His medical history was unremarkable and he denied drug intake. A physical examination revealed multiple, maculopapular and erythema multiforme-like pruritic skin lesions, erythema and oedema of the hands, feet and ears, non-exudative bilateral conjunctivitis, injected lips and strawberry tongue (fig. 1). The oral cavity examination showed enanthema with petechiae and prominent tongue papillae. Symmetric cervical, axillary and inguinal lymphadenopathy was present. Asthenia, myalgia and arthralgia of both small and large joints were present. Diagnosing an allergic disease, the emergency physicians started the treatment with intravenous methylprednisolone (30 mg/kg), and routine laboratory investigations and serology were performed.

Laboratory investigations showed neutrophilic leucocytosis (27.60 × 10^9/l), elevated C-reactive protein (29.1 mg/l) and erythrocyte sedimentation rate (120 mm/h). Serological assays for human immunodeficiency virus (HIV) and hepatotropic viruses were negative, whereas serology for Epstein-Barr virus, morbillivirus, cytomegalovirus and parvovirus B19 was indicative of past immunity. A pharyngeal swab was negative, and the antistreptolysin titre was within normal limits. Skin biopsy revealed no specific histological findings demonstrating a mild hyperplasia of the epidermis and perivascular inflammatory...
infiltrates of lymphocytes in the dermis. Direct immunofluorescence showed deposits of IgM and C3 in dermal vessels.

At the dermatological consultation performed 6 days after the initial examination, the patient partially responded to the corticosteroid therapy but some lesions were still present on the trunk, and a large-scale desquamation of the hands and a mild furfuraceous desquamation on the face were observed (fig. 2, 3). He still complained of fever (38.0°C) and asthenia. Electrocardiogram, chest X-ray and echocardiography were within normal limits. On the basis of clinical presentation and diagnostic criteria, a diagnosis of complete KD was finally made.

A treatment with aspirin (100 mg 3 times daily) was given, and systemic corticosteroids were gradually reduced within 2 weeks. The patient reported clinical improvement and typical desquamation of the palms and soles with complete resolution after 1 month.

Discussion

Adult-onset KD is rarer than in childhood. No specific diagnostic tests are available for KD, and the diagnosis is based on the presence of characteristic clinical findings [3].

It has been hypothesized that KD results from the exposure of a genetically predisposed individual to an as yet unidentified, possibly infectious trigger [4]. Epidemiological data is strongly suggestive of a genetic component to aetiology, with studies worldwide reporting a focal heightened incidence in children of East Asian origin. Linkage analysis and genome-wide association studies have identified several single nucleotide polymorphisms that show an association with genetic susceptibility to KD [4]. It is possible that bacterial or viral infections, superantigens, humoral factors or a combined superantigen conventional peptide antigen response may underlie the onset of the disease [4]. Superantigens implicated in initiating KD are mainly produced by streptococci and staphylococci but other infectious agents such as Mycoplasma and HIV have been suggested [5]. These superantigens may interact directly with class II major histocompatibility complex molecules present on the surface of these cells causing a series of events leading to vasculitis [5]. In fact, initial systemic inflammation leads to the clinical and laboratory features, and local subclinical vascular inflammation may result in vessel damage and remodelling. Initially, activated inflammatory cells, particularly monocytes, macrophages, T cells and, later in the disease, platelets adhere to the endothelial cells that line medium-sized elastic arteries. The endothelium expresses surface molecules that allow leucocytes and platelets to adhere, and some of the adherent inflammatory cells penetrate the vessel wall. Local expression of mediators attracts further inflammatory cells and increases vessel permeability [6]. In addition, Th17/T<sub>reg</sub> imbalance is observed in patients with acute-phase KD. Th17/T<sub>reg</sub> imbalance may be an important factor causing disturbed immunological function. IL-17 induced by Th17 cells has pro-inflammatory properties and acts on inflammatory cells, thereby inducing expression of cytokines and chemokines and resulting in tissue inflammation [7].

One of the currently most accepted theories [8] suggests that the disease may be caused by an infectious agent, probably a virus, which is inhaled and infects medium-sized ciliated bronchial epithelial cells. This non-identified agent is then engulfed by tissue macrophages, and an innate immune response is initiated with subsequent infiltration of macrophages, antigen-specific T lymphocytes and IgA plasma cells. Monocytes and macrophages containing the KD agent enter the bloodstream so that the agent is able to infect specific susceptible tissues (vascular and ductal tissues). In the coronary tissue, the infection leads to the secretion of vascular endothelial growth factor, matrix metalloproteinase 9, tumour necrosis factor-α and other pro-inflammatory cytokines. This immune reaction destroys the intima, internal and external elastic laminae of the coronary artery which are fragmented, and ballooning occurs leading to an artery aneurysm [2].

The low diagnostic accuracy for adult-onset KD, in contrast to that in paediatric patients, can be attributed to the several differential diagnoses [3] that are possible in adult cases (table 1). The diagnosis of KD is usually based on the presence of at least 5 days of fever and 4 of the 5 principal clinical features (table 2) [2]. Indeed, some patients with suspected KD do not fulfil the diagnostic criteria, and diagnosis is made based on coronary artery abnormalities.
These cases would be the so-called ‘incomplete KD’, and it is more frequent in children under 1 year of age [2]. In other studies [9], ‘incomplete KD’ refers to patients with fever lasting ≥5 days and 2 or 3 clinical criteria (rash, conjunctivitis, oral mucosal changes, changes on extremities, adenopathy), without reasonable explanation for the illness. The term ‘atypical KD’ should be reserved for patients who have atypical symptoms that are not common in classical KD, such as renal impairment, acute surgical abdomen and pleural effusion [2]. In these cases, the diagnosis of KD is frequently made retrospectively on the bases of the patient’s history of classical features and symptoms usually in the paediatric age.

Classical KD is unusual in adults, with 81 cases previously reported in the literature since 2010 and 13 cases of incomplete adult-onset KD [1, 3, 9, 10]. Our patient fulfilled the criteria for the classical (typical) KD. Although a scarlatiniform rash is also occasionally reported in KD [11], we considered in the differential diagnosis other hypotheses such as streptococcal scarlet fever or meases. However, the negativity of the pharyngeal swabs and anti-streptolysin titre within normal values ruled out the first possibility and the serological findings the latter.

In the past, KD may have masqueraded as other illnesses, and old reports on infantile polyarteritis nodosa describe pathological findings that are identical to those of fatal KD [11]. In fact, KD may be frequently undiagnosed especially when present in an adult patient and without the presence of all the classical clinical features. Nevertheless, the relatively large series of adult KD highlights the existence of both complete and incomplete KD in adults so an algorithm for the classification of KD in adults is needed. Attention should also be paid to cases of atypical KD because early diagnosis and intervention are crucial for the prevention of cardiovascular morbidity and mortality. In KD, associated treatment with intravenous immunoglobulins (IVIG), aspirin and, possibly, pulse intravenous methylprednisolone is recommended [12]. In adult patients, a current scoring system is still imperfect for predicting an aneurysm. Harada [13] developed a risk score to use in patients presenting KD in childhood to determine the risk of long-term complications such as coronary aneurysms and, furthermore, to improve management of these patients [11]. Four among the following criteria are generally request-
ed: (1) white blood cell count >12,000/ mm³; (2) platelet count <350,000/mm³; (3) C-reactive protein >3+; (4) haematocrit >35%; (5) albumin >3.5 g/dl; (6) age ≤12 months; (7) male sex. In North America, where IVIG is recommended for all children with KD, Beiser et al. [14] developed other classification instruments for predicting the development of coronary artery lesions among treated patients including baseline neutrophil and band counts, haemoglobin concentration, platelet count and temperature on the day after IVIG infusion [11]. However, because of the imperfect performance of scoring systems, all patients who are diagnosed with KD should be treated with IVIG [11]. The disease should be considered the same in adults and children, but given its rarity there is no specific recommendation in adulthood, so we should use the same diagnostic criteria, risk scores and treatment recommendations as used in children [11]. Our patient had 3 (1 + 3 + 7) out of 6 criteria from the Harada score, and electrocardiogram and echocardiography within normal limits, so in this case we decided not to use the IVIG treatment.

Long-term management and cardiovascular risk assessment of patients with KD is very important for the prevention of heart disease [11]. In paediatric patients, a periodic follow-up is very important for the prevention of acquired heart disease. On the other hand, in adults attention should be paid to cases of vascular aneurysms and other complications that could follow a history of suspect KD.

In conclusion, our clinical case represents additional evidence that KD could also occur in adult Caucasian patients with the characteristic classical form of the disease. Nevertheless, the relatively large series of adult KD in the literature highlights the existence of both atypical and incomplete forms in adults. A diagnostic algo-

### Table 1. Differential diagnosis

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<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Drug hypersensitivity reactions</td>
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<td>Toxic shock syndrome</td>
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<tr>
<td>Erythema multiforme and Stevens-Johnson syndrome</td>
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<td>Scarlet fever</td>
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<td>Measles</td>
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<tr>
<td>Rubella</td>
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<tr>
<td>Adenovirus, parvovirus, herpesvirus infection</td>
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<td>Infectious mononucleosis</td>
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<td>Toxoplasmosis</td>
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<tr>
<td>Leptospirosis</td>
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<tr>
<td>Rocky Mountain spotted fever</td>
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<tr>
<td>Systemic juvenile-onset idiopathic arthritis</td>
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<td>Rheumatic fever</td>
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<td>Reiter syndrome</td>
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<td>Mercury poisoning (acrodynia)</td>
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### Table 2. Diagnostic criteria for KD

**Fever of 5 days and presence of 4 principal features:**

1. Changes on the extremities: in the acute phase, erythema of palms and soles, and oedema of hands and feet; in the subacute phase, desquamation of fingers and toes
2. Polymorphous exanthema
3. Bilateral bulbar conjunctival injection
4. Changes of the lips and oral mucosa: erythematous and cracked lips, strawberry tongue, and oral and pharyngeal hyperaemia
5. Cervical lymphadenopathy (>1.5 cm diameter)
6. Pathological changes of the lips and oral mucosa:
   - Erythematous and cracked lips
   - Strawberry tongue
   - Oral and pharyngeal hyperaemia
7. Other classification instruments for predicting the development of coronary artery lesions among treated patients including baseline neutrophil and band counts, haemoglobin concentration, platelet count and temperature on the day after IVIG infusion [11].
algorithm for incomplete and atypical KD should be applied in these patients as well as in children. The additional criteria necessary for the correct evaluation of incomplete forms in children include: clinical assessment, laboratory routine and supplemental tests and echocardiogram consultation [11].

Early diagnosis and intervention are crucial for the prevention of cardiovascular morbidity and mortality in patients with KD diagnosis. Therefore, the diagnostic algorithm for incomplete or atypical KD in adults should be formulated, or the same already adopted for children should be applied.

Disclosure Statement

The authors have no conflict of interest to disclose.

References