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CASE REPORT

Safety netting versus overtreatment in paediatrics: viral infection or incomplete Kawasaki disease?

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SUMMARY

Kawasaki disease (KD) is the most common systemic vasculitis of childhood. The following presentation of a 4-year-old Irish boy referred to a secondary care paediatric service from the community with prolonged fever, oral mucous membrane changes and painless blistering lesions of the hands and feet in the presence of elevated inflammatory markers serves as an opportunity to discuss the diagnostic criteria and treatment for KD and incomplete KD, an often missed diagnosis with significant paediatric morbidity outside an academic paediatric centre.

BACKGROUND

Kawasaki disease (KD) is a systemic vasculitis of childhood identified initially in Japan in the 1960s.¹ Incidence of KD in children aged 5 and under varies worldwide from 4.9 per 100 000 children in Denmark to 211 or more in Japan or those of Japanese descent.^{2–4} The exact aetiology of KD remains unknown.⁵ It is of major concern as 10%–25% of confirmed untreated cases may develop coronary aneurysms and have increased risk of myocardial ischaemia, infarction and sudden death.^{3 6} A subset of incomplete cases who do not meet all established criteria for KD are also recognised in the literature to be at equivalent risk of serious sequelae and are more likely to go untreated.^{6 7} This recognition failure leading to treatment delay increases the risk of immediate and delayed coronary artery aneurysm, which is the leading cause of acquired heart disease in children.^{3 8} The following case of intermittent prolonged fever and rash in a 4-year-old boy illustrates the difficulty clinicians face to treat prophylactically when a common presentation of upper respiratory tract infection partially fulfils the diagnostic criteria for a more severe illness such as incomplete KD (iKD).

CASE PRESENTATION**History**

A 4-year-old white Irish fraternal twin boy was referred to the paediatric service from the community with a history of :

- ▶ 3 weeks of recurrent tonsillitis, coryza and dry cough for ;
- ▶ 2 weeks of painless blistering lesions on hands, feet and mouth (with or without fever) ;
- ▶ 4 days of documented relapsing and remitting fever 39°C in the setting of decreased oral intake.

Of note, his twin sister was hospitalised with similar symptoms for 24 hours prior to the patient and then discharged home. Neither child had vomiting, diarrhoea, meningeal signs, mucositis or strawberry tongue during illness.

Prior medical history

The patient was well prior to admission, up to date with all vaccinations, had no allergies and took no regular medications other than paracetamol and amoxicillin prescribed in the community.

His obstetric, birth history and neonatal course was unremarkable except for an in vitro fertilisation assisted twin pregnancy and C-section for breech presentation at term. His development to date is normal.

Examination at admission was of an afebrile, alert, oriented 4-year-old boy in no acute distress. He weighed 14.7 kg. All other vital signs were within normal parameters for a child of his age.

Examination of the respiratory, cardiovascular and gastrointestinal systems was unremarkable. Examination of the eyes, ears, nose and throat revealed no bulbar conjunctival injection, a right erythematous tympanic membrane, erythematous, congested nasal mucosa and erythematous, inflamed pharyngeal tonsils without exudate.

Musculoskeletal survey and review of systems were also unremarkable.

Intermittent irritability, lethargy and fevers (38°C–39°C) continued for 24 hours after admission. A faint abdominal exanthem and bilateral uniquely cervical lymphadenopathy in addition to erythematous oral mucosa and scattered lower respiratory crepitations were noted at this time.

INVESTIGATIONS

Blood work revealed a neutrophil leucocytosis with elevated inflammatory markers (C reactive protein (CRP) 44.32 mg/L with erythrocyte sedimentation rate (ESR) of 60 mm/hour). Platelets were normal. The patient was not anaemic, but his serum albumin was on the low side of normal. His fibrinogen was mildly elevated and red blood cell count mildly decreased. All other blood work and urine culture were normal.

DIFFERENTIAL DIAGNOSIS

1. Viral upper respiratory tract infection
2. Human adenovirus⁹
3. iKD
4. Juvenile idiopathic arthritis



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5. Acute streptococcal and staphylococcal infections (staphylococcal scalded skin syndrome)
6. Drug hypersensitivity reactions
7. Toxic epidermal necrolysis (aka Steven-Johnston syndrome)¹⁰

TREATMENT, OUTCOME AND FOLLOW-UP

In consultation with paediatric infectious disease specialists, the team treated the patient prophylactically with 2g/kg intravenous immunoglobulin (IVIG) for iKD in combination with continued antibiotics (clarithromycin). Laboratory trends including leucocytosis and a low normal albumin in the setting of prolonged spiking fevers in a 4-year-old boy in a facility without on-site paediatric echocardiography (ECHO) capability led to the decision to treat. While this does not meet supplemental laboratory criteria in the new 2017 guidelines,⁴ the rationale for this decision was that the consequences of missing iKD were thought to be possibly catastrophic in this young child compared with the risks associated with IVIG treatment in the setting of ongoing antibiotics (eg, small risk of aseptic meningitis, haemolytic anaemia). In essence, this is safety netting. In the face of diagnostic uncertainty, the clinician should make the safest decision (aka minimising harm and maximising benefit) while avoiding overtreatment. As there is a known risk of Reye's syndrome with aspirin in an infectious febrile child and thus irreversible neurological sequelae with an unknown treatment benefit, experts initially withheld aspirin.⁵ Treatment was well tolerated by the patient.

The patient was scheduled for cardiology review by paediatric cardiology consultant clinic which occurs biannually and happened to coincide with the patient's discharge date 3 days postadmission. Review at this time revealed possible mild left ventricular hypertrophy on ECG without additional significant changes. Bedside ECHO demonstrated normal coronary arteries and no left ventricular dilation. Findings could not rule out iKD. Paediatric cardiology added a maintenance dose of aspirin 50 mg (3 mg/kg) by mouth daily for easy dosing as the patient was no longer febrile and scheduled the patient for outpatient repeat echocardiography at a tertiary centre in early January 2015 due to risk of late forming coronary aneurysm.

DISCUSSION

Diagnosis

Upper respiratory tract infection coincides with many cases of KD.^{9 11 12} The postulated viral aetiology in genetically susceptible patients means that many features of KD are non-specific indicators of inflammation which could be viral or bacterial in origin.^{2 4} Given the prehospital course, it was unlikely on admission that the patient had an infection of bacterial origin as he had been given three courses of antibiotics that would cover relevant pathogens. The absence of joint involvement make juvenile idiopathic arthritis a less likely differential.^{2 4 6 13} While drug hypersensitivity reactions are always possible, the presentation and lack of mucocutaneous findings, along with the number and type of drugs employed and duration of illness, argue against such differentials.¹⁴ As viral serology, cultures and nucleic acid antigen testing were not available, a viral cause cannot be ruled out with certainty and thus remains the most likely alternative to iKD.¹⁵ Since iKD can only be definitively confirmed on the basis of pathological echocardiography findings which may have been prevented through pre-emptive treatment, it is impossible to be certain to the exact aetiology of this child's illness. Given the risks of treatment outlined briefly above and the discussion below, it is important to examine the rationale for this common treatment dilemma.¹²

KD and incomplete Kawasaki diagnosis

KD is a clinical diagnosis based on prolonged fever of 5 days or more with four of the five principal features including (1) bilateral bulbar conjunctival injection, (2) oral mucous membrane changes including injected or fissured lips, injected pharynx or strawberry tongue, (3) peripheral extremity changes including erythema of palms or soles, oedema of hands or feet (acute phase) and periungual desquamation, (4) polymorphous rash and (5) cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter).^{3 11 12}

The clinical course of KD can be divided into three distinct phases: acute, subacute and convalescent. If possible, it is best to make a diagnosis of KD within 10 days of the onset of illness to prevent coronary sequelae.¹⁰ As principal features often do not usually coincide temporally at presentation, recognition of KD can be very challenging.^{2-4 8}

iKD is even more difficult to recognise definitively for any clinician and is a diagnosis of exclusion confirmed often retrospectively on the basis of coronary sequelae.¹⁶ However, given the severity of complications, it should be considered in any child with prolonged unexplained fever.^{11 12 17}

No laboratory test is pathognomonic for iKD. Findings consistent with iKD include elevated CRP ≥ 3 mg/L or ESR >40 mm/hour. Other supportive findings include: a white cell count of more than 15×10^9 cells/L (neutrophil leucocytosis), normocytic, normochromic anaemia for age, platelet count of more than 450×10^9 cells/L after 7 days of illness, sterile (non-neutrophil) pyuria, elevation of serum aspartate aminotransferase (more than 50 units/L) and serum albumin ≤ 30 g/L.^{2 4 11 12}

The American Heart Association (AHA) algorithm^{2 4} for evaluation of suspected iKD provides a framework for risk stratification to inform clinicians' decision to treat prophylactically. The case outlined had adequate clinical features to entertain a diagnosis of iKD.

Delayed diagnosis of iKD can have profound morbidity.¹⁵ In the presence of risk factors, up to 25% of Europeans can develop both early and late cardiac lesions.^{3 8} In tertiary care centres where initial paediatric echocardiography is available, the presence of echogenic lesions is critical in the decision to treat in the presence of elevated inflammatory markers. Practitioners at secondary care facilities, without access to paediatric echocardiography, face more diagnostic uncertainty. The dilemma to treat or not when algorithms developed at academic centres are predicted on technology or skills not ubiquitously available is not helpful to clinicians in these scenarios resulting in the common practice of safety netting (taking the path where the benefits outweigh the risks); however, abject overtreatment should be avoided.¹²

Treatment of suspected iKD

Hospitalisation and IVIG 2g/kg in a single infusion within the first 7 days of symptoms have been shown to reduce the prevalence of coronary artery abnormalities. Therapy remains effective up to 10 days for clinical onset preventing new coronary abnormalities but does not treat pre-existing aneurysms or plaques.^{12 1} However, risks such as haemolytic anaemia, aseptic meningitis, infection with bloodborne pathogens from human plasma products or Reye's syndrome associated with aspirin administration are infrequent side effects.^{10 12 1}

In this case, while aspirin was withheld initially due to risk of irreversible harms in the setting of unknown benefit, paediatric cardiology did prescribe low-dose aspirin within the 1–5 mg/kg/day for the 4 weeks prior to repeat review for delayed coronary

artery lesions.^{8 12} Of note, the child was afebrile for a significant period when given aspirin diminishing the theoretical risk of Reye's syndrome.¹

While the current recommendation is that all patients who have received treatment should be re-evaluated within 2–6 weeks of baseline echocardiogram, further follow-up may be unrealistic. If no changes are seen initially or in the follow-up echocardiogram, further echocardiography is usually unnecessary,^{2 4} as are activity restrictions or medications beyond 3 months after the initial illness.^{10 12}

CONCLUSION

This case of prolonged fever with features of iKD in a 4-year-old boy has three important learning points: (1) A review of the diagnostic criteria of KD and iKD; (2) the recent AHA treatment algorithms and their limitations in under-resourced or rural areas, in addition to (3) a worked example of the rationale clinicians employ when safety netting in the context of diagnostic uncertainty.

Learning points

- ▶ Kawasaki disease (KD) is the most common systematic vasculitis of childhood with significant paediatric morbidity.
- ▶ Diagnosis of incomplete KD (iKD) is more difficult than its traditional counterpart but should not be missed as these children are at similar risk for serious cardiac sequelae.
- ▶ There are algorithms to assist with the diagnosis of KD and iKD but they may need to be adapted and used with judicious clinical judgement outside an academic centre when paediatric echocardiography is not available.
- ▶ Clinicians must balance the risks and benefits of prophylactic treatment for suspected KD or iKD in context of clinical suspicion in the setting of significant morbidity associated with long-term cardiac sequelae.

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