CASE REPORT

Bacillus Calmette-Guérin reactivation as a sign of incomplete Kawasaki disease

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SUMMARY

Kawasaki disease (KD) is an acute, self-limited, systemic vasculitis of unknown aetiology, extremely rare in infants younger than 6 months old. Younger infants are more likely to present with incomplete KD (IKD) and are at higher risk of developing coronary abnormalities. An early and specific clinical sign, not included in the classical diagnosis criteria, but that can be very useful in the diagnosis of KD, is the reaction at the Bacillus Calmette-Guérin (BCG) inoculation site. We describe a case of a 4-month-old boy, fully immunised, whose BCG scar reactivation led to the diagnosis of IKD. This case-report emphasises the importance of BCG site reactivation in establishing a diagnosis of IKD that clinicians should be aware of, especially in countries where BCG vaccination is still part of the immunisation schedule.

BACKGROUND

Kawasaki disease (KD) is an acute, self-limited, systemic vasculitis of unknown aetiology, which mainly affects children under 5 years of age.¹⁻³

Incomplete KD (IKD), according to the algorithm proposed by American Heart Association, should be suspected in all children with unexplained fever for more than 5 days associated with less than four of the principal features of KD (bilateral bulbar conjunctival injection; oral mucous membrane changes including injected or fissured lips, injected pharynx or strawberry tongue; changes in extremities such as erythema of palms/soles, oedema of hands/feet and periungual desquamation; polymorphous rash; cervical lymphadenopathy).¹ Laboratory findings can help in the diagnosis if elevation of acute phase reactants is associated with at least three supplemental laboratory criteria (hypoalbuminaemia, anaemia for age, elevation of alanine aminotransferase (ALT), thrombocytosis, leucocytosis and sterile pyuria). In the presence of these criteria, treatment with intravenous immunoglobulins and cardiac ultrasound should be performed.¹⁻⁵

Infants less than 6 months old are more likely to present with IKD and are at higher risk of developing coronary abnormalities.^{1-4 6 7} Therefore, early diagnosis and prompt treatment with high-dose intravenous immunoglobulin are important to reduce the prevalence of coronary artery abnormalities in KD.^{1-4 6 7}

An early and specific clinical sign that is not included in the classical diagnosis criteria, but that can be very useful in the diagnosis of KD, is the

reaction at the Bacillus Calmette-Guérin (BCG) inoculation site.^{1-4 8-12}

We describe a case of a 4-month-old boy, fully immunised, whose BCG scar reactivation led to the diagnosis of IKD.

CASE PRESENTATION

A 4-month-old Caucasian male, born to non-consanguineous parents, with an unremarkable past medical history and fully immunised for age, including BCG vaccination at birth, presented at our hospital with a one-day history of high grade fever and irritability. On the day of admission, he also presented with non-bloody diarrhoea. Physical examination revealed a very irritable febrile child, with non-ill appearance without fever and no other significant findings.

Initial screening showed leukocytosis 26 520/ μ L (65% neutrophils; 26.9% lymphocytes), normal platelet count 394 000/ μ L and C reactive protein of 11.2 mg/dL (normal <0.5 mg/dL). A sterile urine specimen was obtained by straight catheterisation and sent to culture. The urinalysis showed pyuria (leucocytes 125/high power field). Chest radiography was normal. After blood culture was taken, the patient was started on empirical parenteral antibiotics (ceftriaxone 80 mg/kg/day) because of suspected bacteraemia.

On day 4 of illness, the fever remained despite 48 h of antibiotic treatment, although the child was well looking when afebrile and the diarrhoea had ceased. Physical examination also revealed marked erythema and induration involving the BCG scar on his upper left arm and a mild bilateral non-exudative conjunctival injection (figure 1). Cardiopulmonary examination was normal and there were no changes on lips, oral mucosa or extremities, and no cervical lymph node enlargement. Meanwhile, his urine culture was contaminated and blood culture remained sterile.

Between day 4 and day 8 of illness, repeated laboratory evaluation showed normocytic anaemia (haemoglobin 7.8 g/dL), leucocytosis 19 050/ μ L (54% neutrophils; 34.7% lymphocytes) and thrombocytosis 848 000/ μ L; a mild elevation of hepatic aminotransferases (ALT 105 U/L, aspartate aminotransferase (AST) 66 U/L) and elevated acute phase reactants (C reactive protein CRP 9 mg/dL; erythrocyte sedimentation rate ESR 65 mm/1st h). The rest of his investigations including renal and electrolyte panel, serum albumin, serum γ glutamyl transpeptidase and immunoglobulin levels were all normal. Abdominal ultrasonography revealed no abnormalities.

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Figure 1 Erythema and induration surrounding Bacille Calmette-Guérin vaccination scar (left deltoid).

On the eighth day of illness, diagnosis of IKD was posed based on the presence of persisting fever for more than 5 days associated with one classic diagnostic criteria (bilateral non-purulent conjunctivitis) and to inflammation of the BCG scar. In addition, increased levels of ESR and CRP with five supplemental laboratory criteria (anaemia for age, ALT elevation, thrombocytosis, leucocytosis and sterile pyuria) also supported IKD diagnosis.

Echocardiography confirmed an aneurysmal dilation of the right main coronary artery with an internal diameter of 3.8 mm, consistent with KD.

The child was then started on intravenous immunoglobulin therapy (IVIG 2 g/kg over 12 h) and acetylsalicylic acid (100 mg/kg/day), and ceftriaxone was discontinued. His fever subsided 24 h after the IVIG. Fever and conjunctival hyperaemia immediately resolved, while the erythema and induration at the BCG vaccination site improved over the subsequent week.

Laboratory findings at second week of illness revealed normocytic anaemia (haemoglobin 8.5 g/dL), white cell count 14 400/ μ L (15.5% neutrophils; 77.1% lymphocytes) and thrombocytosis 1 044 000/ μ L; blood biochemistry with decreased acute phase reactants (C reactive protein PCR 0.1 mg/dL; erythrocyte sedimentation rate 11 mm/1st h) and normal hepatic aminotransferases (ALT 36 U/L, AST 31 U/L).

On day 19th of illness, the patient was discharged home on high-dose aspirin, which was reduced to 5 mg/kg/day after 48 h without fever.

OUTCOME AND FOLLOW-UP

Follow-up echocardiography 4 weeks after disease onset showed right coronary artery ectasia. The convalescent phase was unremarkable and aspirin therapy continued for 8 weeks.

A follow-up examination, conducted 4 months later, showed a normal, healthy infant with no recurrence of symptoms.

Laboratory evaluation revealed no anaemia (haemoglobin 11 g/dL) and a normal platelet count 276 000/ μ L. Echocardiogram was also normal, showing no coronary abnormalities.

DISCUSSION

KD primarily affects young children, with a peak incidence at 2 years of age, but it is uncommon in children younger than 6 months of age, such as our patient.^{1-4 6-7}

Infants under 6 months of age are more likely to have IKD not fulfilling the classical diagnostic criteria.^{4 6-7} In fact, our patient had incomplete presentation of KD, as—besides the presence of fever and nonresponse to antibiotics—he had only one more classical clinical diagnostic criterion, which was bilateral non-exudative conjunctivitis. None of the other clinical criteria, such as diffuse maculopapular erythematous rash, erythema of the lips or oral mucosa, changes on extremities or cervical lymph node enlargement were noticed in our patient. Clinical manifestations of KD vary with age and prevalence of cervical lymphadenopathy or changes on extremities is lower in young patients with KD, especially if less than 2 years of age.^{4 6-7}

In addition to the diagnostic criteria, a broad range of non-specific clinical features, including diarrhoea,¹⁻³ can be observed, which were present in this infant but are also common in other clinical situations.

Although laboratory findings in the acute phase of KD are also non-specific, in children who do not complete diagnostic criteria, they may be useful to support the diagnosis. In this case, among the supplementary laboratory findings, we found leucocytosis (white cell count more than 15 000/ μ L), elevated acute phase reactants (CRP more than 3 mg/dL, ESR more than 40 mm/1st h), elevation of ALT, normochromic, normocytic anaemia for age, sterile pyuria (more than 10 white blood cell/high power field) and thrombocytosis (platelet cell count more than 450 000/ μ L) after 7 days of illness.¹⁻⁵

The diagnosis of IKD was only presumed after 8 days of illness, when the infant had already developed coronary abnormalities, detected on echocardiography. IKD in infants less than 6 months of age is associated with higher risk of developing coronary abnormalities, which may be associated with a diagnosis delay in this type of presentation.^{4 6-7 13} Besides presentation with IKD, other risk factors described as predisposing to cardiovascular sequelae were present in our patient: male gender, normochromic anaemia, elevated C reactive protein and elevated ALT.¹⁻³

Therefore, early diagnosis and prompt treatment with high-dose intravenous immunoglobulin are important to reduce the prevalence of coronary artery abnormalities in KD.¹⁻⁴ Thus, any clinical or laboratory finding that could lead to early diagnosis is worth taking into consideration.

The early recognition of an erythema on BCG inoculation site along with the presence of persistent fever and bilateral non-purulent conjunctivitis could have raised the suspicion of IKD and prompted treatment. Erythema, induration or crust at the BCG inoculation site (BCGitis) has been reported to be an early and useful sign in the identification of IKD cases, especially in countries with national BCG vaccination programme.^{1-4 8-12} It has also been listed by the American Heart Association as a significant finding among the diagnostic guidelines for KD.¹ Rezai and Shahmohammadi,⁸ and Uehara *et al*¹¹ found reactivation of BCG site in 50% of their patients with KD, with a higher proportion of male patients.

The reason for BCG reactivation in children with KD is still unclear, but previous studies have suggested that cross-reactivity

occurs between mycobacterial Heat Shock Protein 65 (HSP65) and the human homologue HSP63.¹⁴ Subsequent studies detected strong antibody and cellular reactivity against HSP65 and its human homologue HSP63 in the peripheral blood of patients with KD.¹⁵

As in our case, Lai *et al*⁹ described that a reaction at the BCG inoculation site developed more frequently in younger patients with KD, especially those aged less than 6 months, and it was also more prevalent in male patients. Rezai and Shahmohammadi,⁸ Lai *et al*⁹ and Uehara *et al*¹¹ also reported that the prevalence of BCGitis is higher than the incidence of cervical lymphadenopathy among patients with KD under 2 years of age.

Therefore, in this case-report, we emphasise the importance of BCG site reactivation in establishing a diagnosis of IKD that clinicians should be aware of, especially in countries where BCG vaccination is still part of the immunisation schedule.

Learning points

- ▶ Kawasaki disease (KD) diagnosis is based on clinical criteria, because there is no specific diagnostic test currently available.
- ▶ In countries where Bacillus Calmette-Guérin (BCG) vaccination is still part of the immunisation schedule, a reaction at the BCG inoculation site may be an early and useful sign of KD cases, especially in patients younger than 6 months old.
- ▶ Even if patients do not fulfil clinical criteria for KD, clinicians should consider the possibility of KD in patients with three or fewer of the clinical criteria but with a reaction at the BCG inoculation site.
- ▶ The recognition of BCG reactivation may facilitate KD early diagnosis and prompt treatment, thus preventing the development of coronary artery abnormalities.

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Competing interests None declared.

Patient consent Obtained.

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