Usefulness of BCG reactivation in Incomplete Kawasaki Disease: A Case Series

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Abstract

Incomplete Kawasaki disease continues to be a major dilemma. Early diagnosis and appropriate intervention is important but clinicians are hampered with the lack of any specific diagnostic aid. Under these circumstances any diagnostic clue should be very useful. We hereby present three case reports wherein BCG scar reactivation helped in formulating a diagnosis of Incomplete Kawasaki.

INTRODUCTION

Kawasaki disease (KD) has become the leading acquired cardiac disorder in the aediatric population in the developed world. Better awareness of this condition as led to increased case reports even from developing countries. Paediatricians ace a clinical dilemma when evaluating a child with features of KD. Failure to ake the diagnosis results in the child being denied a highly effective therapy and reventing subsequent life threatening complications. Conversely, diagnosing KD in child with some other condition means that he/she may not receive appropriate treatment and may be subjected to unnecessary and costly diagnostic and therapeutic interventions . This dilemma is further compounded with increasing reports of incomplete Kawasaki Disease (IKD) ([1]). Cardiovascular complications are most common in young infants and unfortunately it is in this very age group IKD is more frequently reported ([2]). So early diagnosis is extremely important to avoid serious cardiovascular morbidity as well as mortality. Isolated cases of the usefulness of reactivation of the Calmette-Guerin Bacillus (BCG) inoculation scar in the diagnosis of KD has been described in the literature.([3]) .We hereby present 3 cases of incomplete Kawasaki Disease wherein this sign aided us in making an earlier diagnosis. Though all three were of Asian origin, the initial two cases presented in a tertiary setting in India while the last one presented in a District General Hospital in the UK. We believe this to be the first reported case series documenting the usefulness of BCG reactivation in diagnosing IKD.

CASE 1

A 9 month old Indian boy presented with 4 days of fever, irritability and a mild aculopapular rash. Apart from red lips and oral mucosa the only other striking feature was erythema around the BCG scar mark (Table 1). The child was vaccinated at birth and his mother noticed reddening around the scar on day 3 of fever. In view of the irritability and high fever a full septic screen was done (Table 2) and intravenous antibiotics started.

Figure 1

Table 1

Clinical Findings	Case 1	Case 2	Case 3
Age	9 m	7 m	4 m
Sex	M	M	F
Fever >5 days at diagnosis	+	+	+
Non purulent conjunctivitis	-	+	+
Oral mucosa reddening	+	-	+
Peripheral changes	-	+	-
Rash	+	+	+
Cervical lymphadenopathy	-	-	-
Irritability	+	+	+

Figure 2

Table 2

Lab Findings		Case 1	Case 2	Case 3
Hb (g/dl)		9.6	9.2	9.4
ESR (mm/1st hr)		76	84	70
Platelets (00,000/ cu mm)	< 1week	1.6	3.6	2.8
	> 2 week	6.1	6.4	8.2
White Cell Count (/cu mm)		15,000	12,000	16,000
CRP (mg/dl)		45	68	110
Alanine Transferase		22	80	46
Albumin		38	48	34
Urine white cells / high power field		< 10	<10	<10

Persistence of fever even after 48 hours of antibiotics and erythema of the BCG scar in an extremely irritable infant led us to suspect incomplete Kawasaki Disease The child was started on aspirin around day 9 but intravenous immunoglobulin (IVIG) could not be started because of economic constraints . Fever responded slowly over the next week and the BCG erythema disappeared by the end of the second week. Though the echocardiogram done on day 8 was normal a repeat during the third week of illness revealed a dilated left main coronary artery with a diameter of 4 mm. Follow-up echocardiogram at 6 months showed persistence of the coronary artery changes and he continues to have regular cardiac review.

CASE 2

This 7 month old Indian boy presented with 3 days of fever and diarrhoea.

Irritability was the most noticeable feature. Apart from irritability, bilateral non- discharging red eyes and swollen painful feet were the only other positive findings at admission. (Table 1) Intravenous antibiotics were started after a full septic screen (Table2) but the fever persisted. Redness around his BCG scar along with induration was noticed on the fifth day of the illness. Persisting fever, irritability, bilateral non-discharging conjunctivitis, swollen feet, and BCG scar reactivation led us to suspect incomplete KD. IVIG was started on day 6. Fever subsided within a day of this and erythema and induration around the BCG scar disappeared in another 24 hours. Repeat echocardiogram at 6 weeks revealed a left coronary artery diameter of 2.5 mm which persisted until the last scan at the age of 18 months .

CASE 3

A 16 week old female of Chinese origin presented with a history of persistent fever for 3 days. She was very irritable and had bright red lips, red eyes with a few blanching maculo-papular spots on the trunk (Table 1). Intravenous antibiotic was started after a full septic screen (Table 2). The baby continued to have a very high spiking temperature even after 48 hours of antibiotics. Subsequently marked redness with some induration was noticed around the BCG site. Due to the presence of fever for over 5 days, conjunctivitis & red lips in an irritable child incomplete KD was being contemplated . This was further strengthened by the development of erythema around the BCG scar . The child was started on IVIG to which the fever showed a remarkable response within 36 hours . Erythema around the BCG site also disappeared simultaneously . Her initial echocardiogram has been normal and she is under cardiac follow up.

DISCUSSION

The principal clinical findings in KD, the second most common vasculitis in childhood, are fever, bilateral non - exudative conjunctivitis, erythema of lips / oral mucosa, changes of extremities, rash, and cervical lymphadenopathy . Fever with at least four of the five principal clinical findings are needed for its diagnosis(4) The etiology of Kawasaki disease remains unknown, although clinical and epidemiological features strongly suggest an infectious cause, though efforts to identify an infectious agent has not been productive. Various hypothesis has been

floated including the attractive superantigen theory supported by selective expansion of V□_2 and V□_8 T-cell receptor families (2). Recent research has suggested alternative hypothesis with a likelihood of oligoclonal immune response rather than polyclonal (superantigen) and a key role for IgA plasma cell response (5)

Some patients lack sufficient clinical signs (fewer than four out of five principal clinical findings) to fulfil the classic criteria and are diagnosed as having KD (2). IKD is an independent risk factor for subsequent coronary artery ectasia and early treatment with IVIG has been shown to lower its risk. (2). This underlies the necessity of early diagnosis and the need for a low index of suspicion. IKD should be considered in all children with unexplained fever for ≥ 5 days with 2 or 3 of the principal clinical features of classical Kawasaki Disease.(2)

Keeping the importance of early diagnosis in mind, any system which aids this justifies attention. Though the usefulness of BCG reactivation is still not mentioned in standard text books (4) it has been well described as a specific sign of KD.([3])

BCG scar erythema in KD has been hypothetically ascribed to cross-reactivity between mycobacterial Heat Shock Protein (HSP) 65 and Human Homologue HSP63,a mitochondrial protein. The detection of strong antibody and cellular reactivity against synthetic peptides of mycobacterial HSP65 and its human homologue in the blood of children with KD agrees well with this hypothesis ([6]) . Bertototo et al has shown the presence of strongly positive tuberculin test in his population of children with Kawasaki Disease and have suggested further studies in its use as a diagnostic aid in IKD ([7]).

Very few isolated case reports are available about the presence of BCG reactivation erythema in IKD . The present case series documents usefulness of BCG inoculation site reactivation in establishing a diagnosis of IKD. None of these infants showed more than three classical criteria though they did have fever not responding to antibiotics and increased inflammatory markers (Table 1 & 2). The recently published statement on KD endorsed by the AAP does focus on similar clinical dilemmas and suggested a flowchart as an aid to early diagnosis of IKD ([2]) . Though this flow chart will decrease the likelihood of missing IKD even the panel admitted the increased possibility of over treatment and its yet to be determined consequences ([2]). Under such circumstance presence of an extra validated early diagnostic sign should definitely be useful.

We hope that this article will encourage more studies into the possibility of diagnosing KD/IKD based on BCG reactivation. At the same time studies are also needed to evaluate the usefulness of the tuberculin test as diagnostic test in communities where BCG is not universal.

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