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Case Report: A Clinical Dilemma of Diagnosing Recurrent Incomplete Kawasaki Disease

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1. Abstarct

Kawasaki disease (KD) is one of the most common etiologies of acquired heart disease among children worldwide with unknown pathogen. Early recognition and establishing the diagnosis help the clinical pediatrics practitioner delivering intravenous immunoglobulin treatment promptly, which plays the most important part of reducing the risk of developing coronary artery abnormalities. Recurrent KD is not uncommon, and needs to be carefully differentiated from various pathogen. Since the diagnosis based on patient's clinical presentations, incomplete or atypical KD has dramatically increased the difficulties of diagnosis. Some laboratory or clinical findings have been proposed to be efficient indicators of KD, such as erythema, induration, and central crust over the Bacille Calmette-Guérin (BCG) vaccination site, one of the most prominent KD patients' features in vaccinated countries. Here we reported a 1-year-and-8-month child with his first incomplete KD and the recurrent episodes, showing the variant appearance and clinical significance of BCG inoculation site reactivation, and how a pediatric specialist gets to the final diagnosis of KD.

2. Introduction

Kawasaki disease (KD), formerly known as mucocutaneous lymph node syndrome and infantile polyarteritis nodosa, is an acute, medium-sized vessel vasculitis of unknown etiology that may cause coronary artery abnormality (CAA), and the diagnosis is based on some chief clinical findings. According to the guidelines denoted by the American Heart Association, the diagnostic criteria for KD includes fever for at least five days, accompanying with a minimum of four of five principal clinical symptoms: 1)polymorphous skin rash over the torso especially in the groin area, 2)erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase, 3)bilateral bulbar conjunctival injection without exudate, 4)cervical lymphadenopathy measuring more than 1.5 centimeters, 5)erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa [1]. Such symptoms may not present concurrently, and may express at different intervals throughout the disease course. However, not all patients will satisfy the four of five of the aforementioned principal symptoms, may not present four or more symptoms, thus the diagnostic process can be somewhat ambiguous. In such situations, if less than four of the principal symptoms are present, diagnosis can be established with positive detection of CAA on two-dimensional echocardiography, or satisfying at least three supportive laboratory criteria (anemia for age, platelet counts ≥450,000 after the seventh day of fever, albumin ≤3.0 g/dl, elevated alanine aminotransferase (ALT), white blood cell count ≥15,000/mm3, or urine with ≥10 white blood cell/HPF) [2]. Another significant clinical feature of KD is an erythema at the Bacille Calmette-Guérin (BCG) inoculation site which occurs frequently in younger KD patients, especially for those younger than 20 months [3].

Early initiation of intravenous immunoglobulin (IVIG) is strongly recommended in acute phase of KD, which has shown great clinical effect of lowering the risk of developing new or persistent CAA. Regardless of some debate that whether receiving IVIG is a risk factor of recurrence or not, it's still first-line treatment cur-

rently on worldwide. Since the importance of early suspicions may indirectly prompt to early IVIG treatment, the detection and diagnostic accuracy of KD cannot be underestimated. Some reports have shown higher recurrent incidence of incomplete KD than typical KD [4], which dramatically increased the clinical arduousness of making diagnosis among those small group of recurrent cases. Here we present how the clinician chipped away every possibility to get down to the final diagnosis of KD with a 1-year-8-month child of previous incomplete KD history, coming with intermittent fever, mild diarrhea, conjunctivitis and mild BCG erythema.

3. Case Presentation

A 9-month-old boy presented with intermittent fever refractory to antipyretics (up to 38.5 degrees) for 4 days, decreased spirits and appetite, irritable mood, accompanied with erythema, induration, and central crust over his Bacille Calmette-Guérin (BCG) vaccination site (Figure.1 A). The patient's vital signs were stable except for a mild fever up to 37.4ºC. Non-exudative bilateral conjunctivitis (Figure.1 B), and fissured lips were also noted. Skin examination revealed no bilateral palms and soles redness swelling and generalized polymorphic skin rash. In addition, there was no cervical lymph node enlargement or other significant findings on his physical examination. Blood laboratory examinations indicated elevated C-reactive protein (1.676 mg/dl), leukocytosis with left shift (WBC: 18,480/ul, band form: 0.9%, Seg 43%), and thrombocytosis (530,000/ul). Other data revealed hemoglobin (Hb) 11.5 g/dl, hematocrit (Hct) 35.3%, mean corpuscular volume (MCV) 77.2fl, mean corpuscular hemoglobin (MCH) 25.2Pg, monocyte 14%, absolute neutrophil count (ANC) 8,113/ul, sodium 134mmol/l, potassium 4.9mmol/l, alanine aminotransferase (ALT) 19IU/l. Routine urine microscopy was normal and blood culture did not reveal any microorganism growth. On the fifth day after his fever onset, an echocardiogram was arranged for assessing baseline coronary vessels status under the suspicion of incomplete KD. Left main coronary artery dilatation with a small aneurysm (left coronary artery/left anterior descending/right coronary artery diameters: 2.7/1.7/2.2mm; z-scores of left coronary artery/left anterior descending/right coronary artery: +2.9/+1.2/+2.3) and minimal pericardial effusion was detected. Clinical diagnosis of incomplete KD was compatible with echocardiography findings. Treatment of IVIG (2 g/kg) and moderate-dose aspirin (30-50 mg/kg/day) thus started on the next day. The patient's crusted lip and conjunctivitis gradually subsided along with his fever and erythema over the BCG scar. The patient was discharged due to stable conditions and was under low-dose (3-5mg/kg/day) aspirin. Periungual desquamation was reported after being discharged. Echocardiography during a 2-month outpatient follow-up revealed a reduction in left coronary artery dilation (1.9 mm) and no notable pericardial effusion, thus the low-dose aspirin was discontinued (Figure 1).

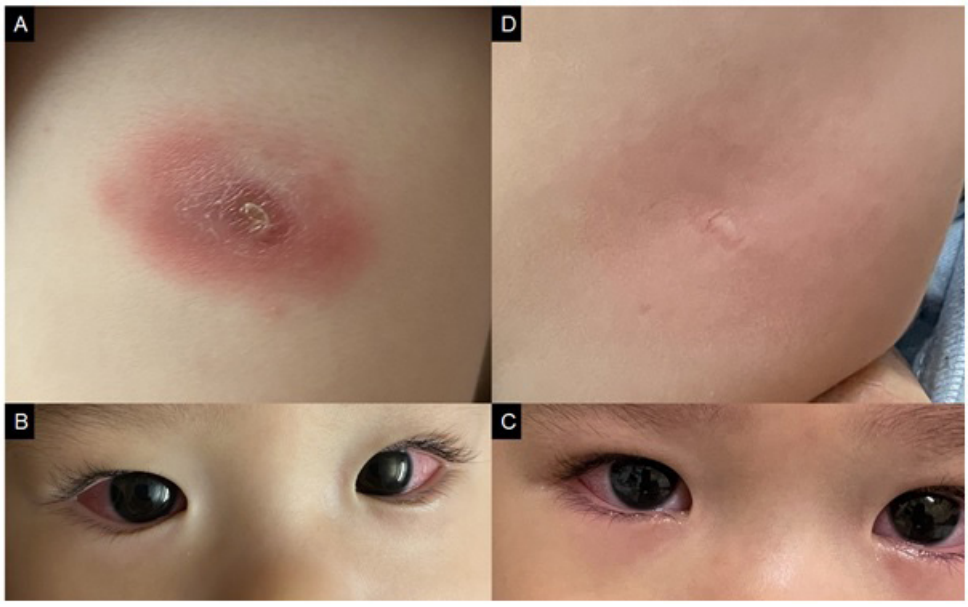

Figure 1: (A) Central crust over Bacille Calmette-Guérin (BCG) vaccination site and (B) bilateral non-exudative conjunctivitis in the patient's first episode. (C) Bilateral non-exudative conjunctivitis along with (D) mild erythema around BCG inoculation site were presented at the second time.

The child returned to our hospital at 1 year and 8 months of age (after 11 months of his first episode) with intermittent fever up to 39.1 degrees Celsius for 2 days, which poorly responded to antipyretics, accompanied with diarrhea for 1 day. The patient's general appearance was irritable. His throat and tonsil were mildly injected; but ulcers, enanthem and erythematous lips were not noted. Bilateral non-purulent conjunctivitis with limbal sparing (Figure.1 C) and mild erythema around BCG inoculation site (Figure.1 D) were presented. There were no significant findings during his physical examination. Hematological investigations showed ele-

vated C-reactive protein (2.892mg/dl), leukocytosis with left shift (WBC: 12,260/ul, Seg 64.4%), thrombocytosis (429,000/ul), Hb 11.6 g/dl, Hct 34.7%, MCV 76.3fl, MCH 25.5Pg, ANC 7,895/ul, ALT 20 IU/l; routine urine analysis and blood culture were sterile. Due to symptoms of fever, diarrhea and conjunctivitis, adenovirus infection was suspected and thus initially treated with supportive care. Respiratory panel screening was arranged and revealed positive results for rhinovirus and enterovirus infection, but adenovirus was not detected. Echocardiogram was arranged on the fourth day of fever onset for regular follow-up (scheduled before his current episode), and showed no significant progression of coronary artery dilation. Despite the patient's improvement of diarrhea and fever, decreased peak temperature and prolonged intervals, irritability and conjunctivitis were still noted accompanied with a new onset of maculopapular skin rash over his trunk and back region when febrile (Figure.2 E). He developed symptoms of fissure and crusty lips on the seventh day of illness. Follow-up laboratory data disclosed further elevated C-reactive protein (from 2.8 to 4.1mg/dl), erythrocyte sedimentation rate (ESR) 75mm/hr, troponin=I 2.8pg/mL, and progressed thrombocytosis (450,000/ul). Furthermore, the patient's parents were unwilling to postpone the vaccination course due to the IVIG injection and asked for conservative treatment with close observation. On the ninth day, his fever had further subsided and laboratory tests had revealed decreased C-reactive protein (from 4.1 to 2.8 mg/dl), but the leukocytosis with left shift (WBC=16,760/ul with band 0.8%, Seg 51.7 %), thrombocytosis (733,000/ul) and ANC (8790/ul) were still noted (Figure 2).

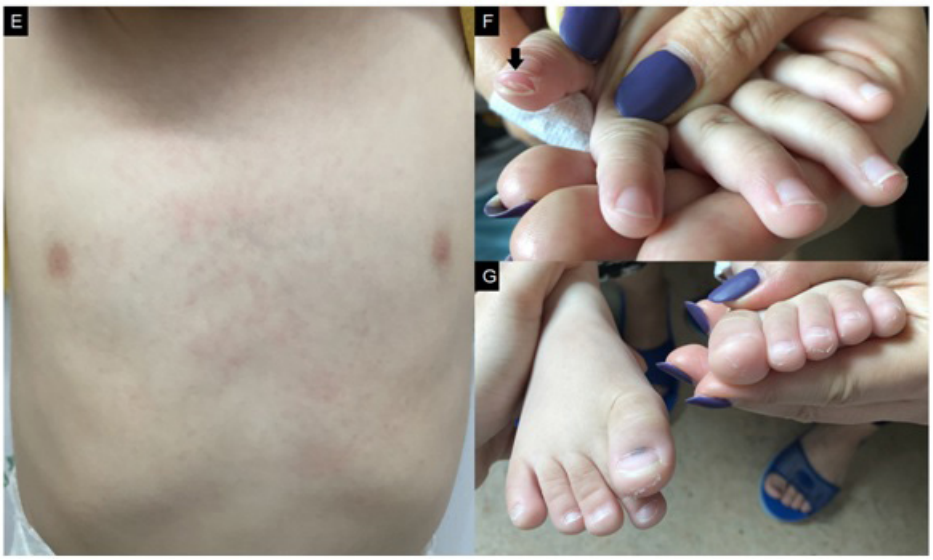

Figure 2: (E) Skin rash when febrile emerged with (F) mild periungual desquamation over the left index (arrow), and ring finger, and (G) atypical skin peeling of bilateral toes in his second episode.

Given the deteriorating hematological findings correlated with constant clinical presentations, the patient met the diagnosis of recurrent incomplete KD and thus started IVIG injection after discussion with his parents immediately. Fever flared up once after IVIG injection but subsided spontaneously within 36 hours. Other associated symptoms including conjunctivitis, fissure and crusty lips, skin rash, and BCG erythematous change were all relieved afterwards. Mild periungual desquamation over the left index and ring finger (Figure.2 F) were reported along with some atypical skin peeling started from bilateral heels to toes (Figure.2 G). Under the stable clinical conditions, the patient was discharged with low-dose aspirin and was scheduled for regular echocardiogram follow-up at the outpatient department.

4. Discussion

Kawasaki disease (KD) is an acute, self-limiting, systemic vasculitis occurring mostly in children younger than the age of five. Patients with KD are at risk of developing cardiac sequelae, especially coronary artery abnormalities (CAA), which ranges from dilation to aneurysm formation, and myocardial ischemia, cause profound clinical impacts and has become the leading cause of acquired heart disease among children in most developed countries [5]. Fortunately, commencing intravenous immunoglobulin (IVIG) injection during the acute phase of the disease can dramatically reduce the risk of developing CAA from 25% of untreated patients to less than 5% [2,6]. Typical KD diagnosis is generally made clinically based on AHA diagnostic guidelines after exclusion of diseases with similar clinical presentations, but up to 25% of KD cases are incomplete or 'atypical' and have a higher risk of complications [7]. Other associated symptoms were proposed to help differential diagnosis and raised early suspicions, but a general consensus has not yet been reached. There are several diseases need to be ruled out before establishing a diagnosis of KD. For this case, during his second episode, streptococcus infection was unlikely due to the hematological results. Ocular manifestations are also rarely seen in streptococcus infections [2]. Additionally,

no skin rash was present upon admission, thus measles, Rocky Mountain spotted fever, scarlet fever, and polyarteritis nodosa were less likely. Systemic-onset juvenile idiopathic arthritis (sJIA) was also excluded for lack of joint swelling, joint pain, and skin rash. Viral infection was initially suspected based on the patient's mild injected throat, diarrhea, and conjunctivitis. Although patient had intermittent high fever, conjunctivitis, skin rash, gastrointestinal symptom, elevated C-reactive protein and ESR but the negative RT- PCR for SARS-CoV-2 was noted, so multisystem inflammation syndrome (MIS-C) could be rule out [8]. Supportive and symptomatic treatment were applied first. Diarrhea improved soon but fever and conjunctivitis persisted. Febrile skin rash then appeared, and crusted lip developed on the seventh day of illness. Recurrent KD was suspected and IVIG was given.

Recurrence of KD is defined as a repeated episode of complete or incomplete KD after complete remission for at least 2 months since the first episode [9]. Recurrence rates seem to be highest for patients younger than the age of 3 and more prominent for those who are younger than 1-year-old or have had cardiac sequelae after their first attack [10]. Higher incidence of recurrent KD was noted within the first year after the first episodes compared to that after 1 year. Other risk factors that can be used to predict the recurrence include: male gender, treatment with IVIG, longer duration of fever, lower hemoglobin levels, and high transaminitis of the first episode [11]. General incidence of recurrent KD remains uncertain, but is around 3% according to a nationwide report in Japan, the first country to discover the disease and has the most cases and detailed reports [10,12]. Taiwan has the third highest incidence of KD worldwide, behind Japan and Korea [13]. The proportion of recurrent cases among children with a history of KD is about 1.5% in Taiwan [14]. For our case, the patient was diagnosed with recurrent incomplete KD with a history of incomplete KD. Of the aforementioned risk factors of recurrence, the patient coincided with a younger age (≦3 years old), male sex, formerly treated with IVIG, and having cardiac sequelae during his first episode. Borderline anemia for age (11.5 mg/dl) was noted, but no liver enzyme elevation nor a prolonged fever duration were observed during his first illness. The episodes fulfilled two out of five and three out of five classic symptoms, respectively, before initiating IVIG injection shared the same features of BCG site erythema (BCGitis). For this case, atypical symptoms (possibly due to a concurrent viral infection of rhinovirus and/or enterovirus) had confounded us initially. However, symptoms such as persistent, non-purulent conjunctivitis, BCG-itis, transient skin rash when febrile, and a new onset fissure and crusty lips raised our suspicion for KD recurrence. This was later supported with aggravated thrombocytosis and an elevated ESR. Subsequent periungual desquamation, improvement of irritable mood, and resolved conjunctivitis have further confirmed the KD diagnosis. Notably, persistent fever had gradually subsided spontaneously before IVIG was given. Later febrile event happened within 24 hours but regressed soon, showing no signs of refractory KD. Persistent fever refractory to antipyretics is the most common and definite diagnostic criteria of complete and incomplete KD, but the self-limiting characteristics of KD may also demonstrate an improved fever pattern and thus increase the clinical difficulty in differentiating some pathogens with similar clinical presentations. Other accompanied symptoms or laboratory findings hence become important for early diagnosis, since IVIG treatment given in the first ten days was shown to improve the patients' prognosis and decrease CAA [15]. BCG scar reactivation has been proposed as a useful feature for early diagnosis of Kawasaki disease, especially in its incomplete form, and in countries where the vaccine is routinely given (e.g. Japan, Korea, and Taiwan) [16]. It has also been reported with higher prevalence among KD patients than cervical lymphadenopathy [17]. Several possible mechanisms have been proposed, with a majority related to cross-reactions between the mycobacterium heat shock protein 65 (HSP65) and the human analog HSP63 [18,19]. Mostly, it appeared to be well-marginated with obvious erythematous change and induration, or some may even show a central crust. Our patient demonstrated the above typical BCGitis findings on his first illness, but variability appeared this time with just mild homogeneous erythema. Differences of the BCGitis demonstrated by our patient in his first and second episodes probably indicate the evolving immunological reaction after the vaccination or exposure.

In summary, this is a case of recurrent KD in incomplete type with previously incomplete KD history. The Erythema of BCG inoculation site is the sharing feature that helps establishing the diagnosis in our case. Different presentations of BCG reactivation may result from the immunological reaction in progress related to the timing of vaccination or exposure. Gradually resolving fever observed in our cases may be due to the self-limiting traits of KD, and thus caused a clinical dilemma of establishing the diagnosis. Clinical practitioners should always highly suspect KD when there are no other diseases that can emphasize the patients' clinical findings, especially in patients with recurrent risk factors of KD history, or if some specific clinical or laboratory findings appeared.

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