

CASE REPORT

 OPEN ACCESS

Two infants with tuberculid associated with Kawasaki disease

Hiroko Yamada^{a,#}, Haruka Ohta^{a,#}, Shunji Hasegawa^a, Yoshihiro Azuma^a, Masanari Hasegawa^b, Ryo Kadoya^c, Noriko Ohbuchi^c, Yuji Ohnishi^a, Seigo Okada^a, Madoka Hoshide^a, and Shouichi Ohga^a

^aDepartment of Pediatrics, Yamaguchi University Graduate School of Medicine, Ube, Japan; ^bDivision of Pediatrics, Yamaguchi Grand Medical Center, Hofu, Japan; ^cDivision of Pediatrics, Yamaguchi Red Cross Hospital, Yamaguchi, Japan

ABSTRACT

Bacille de Calmette et Guerin (BCG) is the only licensed tuberculosis vaccine to prevent severe tuberculosis. The adverse events of BCG vaccination, including local reactions, lymphadenitis, osteomyelitis, tuberculid, and disseminated infection, have been reported. Two infants presented erythema at the inoculation site of BCG after the resolution of Kawasaki disease (K_D). They received BCG vaccination 1 week and 6 weeks before the K_D onset, respectively. Intravenous immunoglobulin improved the K_D activity, however the skin rash of BCG inoculation site extended to the face and extremities days 24 and 10 after the K_D onset, respectively. Both bacteriological study and interferon- γ release assay were negative for *Mycobacterium tuberculosis* infection. These patients were diagnosed as having tuberculid after K_D. The skin lesions gradually disappeared without antibiotic therapy over 2 months. The development of tuberculid in these patients might be associated with the remnant immune activation of K_D.

ARTICLE HISTORY

Received 26 May 2016
Revised 18 June 2016
Accepted 26 June 2016

KEYWORDS

children; Bacille de Calmette et Guerin (BCG); Kawasaki disease; tuberculid; vaccination

Introduction

Bacille de Calmette et Guerin (BCG) vaccine is the only available vaccine for the prevention of severe and disseminated tuberculosis.¹ Local reactions, lymphadenitis, osteomyelitis, tuberculid (erythema induratum, lichen scrofulosorum, and papulonectrotic tuberculid), and disseminated infection have been reported as the adverse events following BCG vaccination.¹

Kawasaki disease (K_D) is an acute, febrile, and systemic vasculitis primarily occurring in infants and young children.² The incidence of K_D is different among ethnic groups, and the highest incidence is reported in Japan (239/100,000 < 5 y of age).² The most serious complication is coronary arterial lesion (CAL).² Intravenous immunoglobulin (IVIG) and oral aspirin are effectively used during the acute phase of K_D to reduce inflammation, particularly CAL.^{2,3} Prior to the introduction of IVIG, 20–30% of cases progressed to CAL, with 2% of mortality rate.³ The etiology of K_D is still unknown, however it may be caused by an infectious agent that precipitates an excessive auto-inflammation in genetically predisposed individuals.^{2,4} Additionally, the changes at the inoculation site of BCG, including erythema or ulceration, are often observed during the acute phase of K_D.^{5,6} BCG triggers apoptosis of tumor cells and promotes T cell activation responsible for long-term anti-tumor defense. These suggest that BCG response may be connected with the pathophysiology of K_D.


Tuberculid including erythema induratum, lichen scrofulosorum, and papulonectrotic tuberculid, is one of the frequent adverse events of BCG vaccination. Affected patients present with dull red or bluish red nodules (erythema induratum), pin head-size, skin-colored, to erythematous lichenoid, firm, follicular or perifollicular papules (lichen scrofulosorum), and papulonodular lesions (papulonectrotic tuberculid).⁷ The skin lesions usually emerge from 10 d to 2 months after vaccination.⁸ The mechanism of tuberculid is considered the skin reactions against BCG vaccine and/or immune responses to degenerated dead bacilli or antigenic fragments,^{8,9} because the lesions are negative for bacteria. However, there is little information about the detailed pathophysiology of tuberculid. It is critical to distinguish tuberculid from disseminated BCG infection or cutaneous tuberculosis. Neither antibiotics nor anti-tuberculous therapy is needed for the treatment of tuberculid.

There are no reports about a relationship between tuberculid and K_D. We herein first report 2 infants who developed tuberculid during the convalescent phase of K_D.

Patient presentation

Patient 1

A 5 month-old Japanese male was hospitalized because of 5-days' high fever, erythema of the trunk, and conjunctival hyperemia. On admission, he had redness of lip, and swelling

CONTACT Shunji Hasegawa, MD, PhD  shunji@yamaguchi-u.ac.jp  Department of Pediatrics, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, 755-8505, Japan.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/khvi.

[#]H. Y. and H. O. contributed equally to this report.

© 2016 Hiroko Yamada, Haruka Ohta, Shunji Hasegawa, Yoshihiro Azuma, Masanari Hasegawa, Ryo Kadoya, Noriko Ohbuchi, Yuji Ohnishi, Seigo Okada, Madoka Hoshide, and Shouichi Ohga. Published with license by Taylor & Francis.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The moral rights of the named author(s) have been asserted.

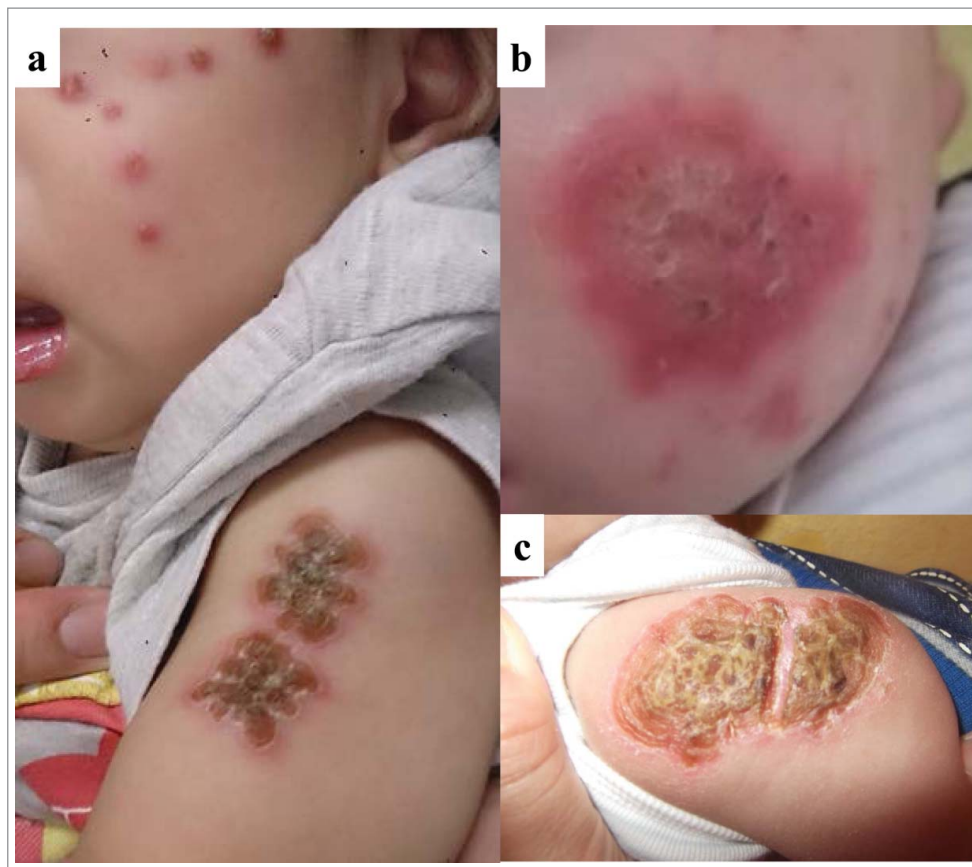


Figure 1. Rash of cheek and BCG inoculation site on day 43 in patient 1 (a), and cheek (b) and BCG inoculation site (c) on day 23 of K_D onset in patient 2.

of feet and hands. The previously healthy boy was born to healthy parents having unremarkable family history. He received BCG vaccination intradermally at the left upper limb one week before the onset of K_D . Complete blood counts showed leukocytes 22.2×10^9 /L, hemoglobin 11.1 g/dL, and platelets 416×10^9 /L. Blood chemistries revealed increased levels of C-reactive protein (CRP) (1.31 mg/dL, reference range [rr]: 0.01–0.14), and normal levels of aspartate transaminase (AST) 31 U/L (rr: 13–33), alanine transaminase (ALT) 15 U/L (rr: 8–42), albumin 4.2 g/dL (rr: 3.7–5.2), and sodium 138 mmol/L (rr: 135–148). Under the diagnosis of K_D , IVIG (2 g/kg) and aspirin (30 mg/kg, p.o.) were started on the 5th day of illness. The treatment led to the defervescence promptly, and sheet-like desquamation on the 9th day, respectively. On the day 25, small papules in the face and trunks, along with redness and crust formation at the inoculation site of BCG were observed (Fig. 1a). Skin biopsy revealed infiltration of inflammatory cells, ulceration, and crust formation without granuloma and leukocytoclastic vasculitis (Fig. 2a and b). Both bacteriological examination from skin lesions and interferon- γ release assay (IGRA) against *Mycobacterium tuberculosis* were negative. These results suggested that he had papulonecrotic tuberculid associated with BCG inoculation. The skin lesions disappeared without antibiotic therapy over 2 months. His nails became whitish, and were peeled off 45 d after K_D onset (Fig. 3a). These manifestations completely resolved 73 d after the onset of K_D . He is alive and well without CAL one year after the hospital discharge.

Patient 2

A 5 month-old Japanese male was hospitalized because of fever, redness at the BCG inoculation site, and redness of the lips. The previously healthy boy was born to healthy parents having unremarkable family history. He received BCG vaccination intradermally at the left upper limb before 6 weeks of the K_D onset. On admission, he showed neither redness nor ulceration at BCG inoculation site. Complete blood counts showed leukocytes 14.4×10^9 /L, hemoglobin 10.4 g/dL, and platelets 274×10^9 /L. Blood chemistries revealed increased levels of AST 298 U/L (rr: 12–34) and ALT 61 U/L (rr: 5–43), CRP (18.14 mg/dL, rr: 0.01–0.14), and procalcitonin (1.58 ng/mL, rr: 0.00–0.10), low levels of sodium (132 mmol/L, rr: 137–147). On the day 4th of illness, he had conjunctival hyperemia, erythema of the trunk of the body, and swelling of feet and hands. Under the diagnosis of K_D , IVIG (2 g/kg) and oral aspirin (30 mg/kg) were started on the 5th day of illness, but not led to the defervescence. Repeated IVIG on the 7th day of illness led to the complete resolution of K_D symptoms. On the 10th day of K_D , erythema in bilateral cheeks and blood clot and crust formation at the inoculation site of BCG were observed (Fig. 1b and c). Skin biopsy revealed infiltration of inflammatory cells, acanthosis, and epithelioid granuloma without caseous necrosis (Fig. 2c and d). Both bacteriological examination from skin lesions and IGRA were negative. These results suggested that he had lichen scrofulosorum. The skin lesions were gradually disappeared without administration of antibiotics over 2 months. His nails changed during tuberculid

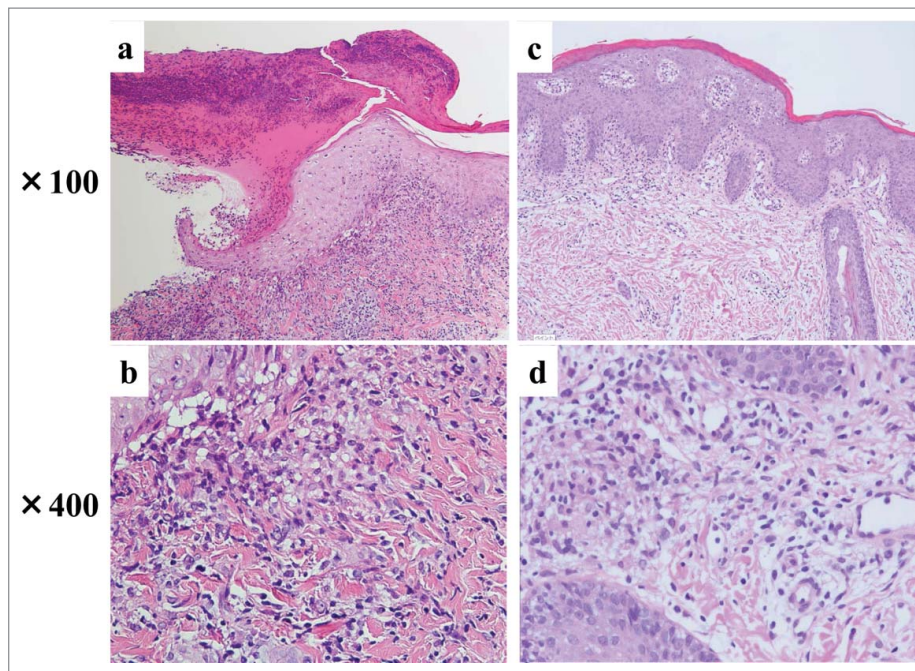


Figure 2. Histopathological finding of skin biopsy from patients 1 (H & E; a: $\times 100$, b: $\times 400$) and 2 (H & E; c: $\times 100$, d: $\times 400$).

(Fig. 3b). He is alive and well without CAL one year after the hospital discharge.

Discussion

Skin complications including tuberculid are occasional adverse events of BCG vaccination. The incidence of tuberculid was extremely low, because the infants with tuberculid after BCG vaccination were reported to be 10–20 per 1 million inoculations in Japan.¹⁰ In our infants, the onsets of tuberculid were observed 10 d (patient 1) or 24 d (patient 2) after onset of K_D . Redness, crust formation, and ulceration of BCG inoculation

site are occasionally observed during acute phase in K_D patients.^{5,6,11} The mechanism of changes at BCG inoculation sites remains unclear, however Siresi, et al.¹² reported that T cell activation, and cross-reactivity between specific epitopes of mycobacterial and human Heat Shock Protein (HSP) may be involved in the changes of BCG inoculation site. In present cases, subsequent immune activation of K_D might be a trigger of the onset of tuberculid. The changes at BCG inoculation site in young infants with K_D could be linked to the pathophysiology of tuberculid.

Both present cases received BCG vaccination 1.5 months (patient 1) or one week (patient 2) before the onset of K_D ,



Figure 3. The changes of nails on day 45 of K_D onset in patient 1 (a) and in convalescent phase K_D of patient 2 (b).

respectively. The relationship between the development of K_D and vaccination is controversial. Previous reports have shown that K_D was developed after the vaccinations of BCG, diphtheria–pertussis–tetanus (DPT), hepatitis A, hepatitis B, influenza, and rotavirus.^{4,13–18} On the other hand, vaccinations do not increase the risk of K_D .^{18,19} In our infants, we could not prove the relationship between BCG inoculation and the onset of K_D .

Both infants with tuberculid showed changes of the color and hypertrophy of nails and their nails were peered off since the convalescent phases of K_D , as shown in Figure 3. There are no reports about changes of the nails in infants with tuberculid. The mechanism of the nail changes in patients with tuberculid with K_D is still unknown. However, it may be similar to sheet-like desquamation in K_D patients, because they started after the convalescent phase of K_D . These nail changes may be a specific symptom in infants with tuberculid associated with K_D .

There have been several reports about tuberculid after BCG vaccination.^{8–10,20–22} All children with tuberculid after BCG were reported to be previously healthy. On the other hand, disseminated BCG infection, which we need to distinguish from tuberculid, often appears under the impaired immune system.²³ The patients' age were 3, 6, 6, 8, 9, 9 month-old, 2 and 7 year-old, respectively.^{8–10,20–22,24,25} In Japan, children generally received BCG vaccination before 1 y old. In addition, 80% of K_D cases occur between the ages 6 months and 4 y.¹ Our observations in these cases suggested a possible association among the age of BCG vaccination, the K_D onset, and the development of tuberculid.

We herein first report two 5-month-old infants with tuberculid after resolution of K_D symptoms. The present patients suggest there may be relationships between the onset of tuberculid and the pathophysiology of K_D .

Abbreviations

BCG	Bacille de Calmette et Guerin
IVIG	intravenous immunoglobulin
K_D	Kawasaki disease
IGRA	interferon- γ release assay

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Contributions to authorship

H.Y., S.H., and S.O. were the principal investigators taking primary responsibility for the paper and wrote the paper. H.Y., H.O., Y.A., M.H., R.K., N.O., Y.O., S.O., and M.H. treated the patients.

References

- [1] Dierig A, Tebruegge M, Krivec U, Heininger U, Ritz N; Paediatric Tuberculosis Network European Trials group (ptbnet). Current status of Bacille

- Calmette Guérin (BCG) immunisation in Europe - A ptbnet survey and review of current guidelines. *Vaccine* 2015; 33(38):4994-9; PMID:26151543; <http://dx.doi.org/10.1016/j.vaccine.2015.06.097>
- [2] Greco A, De Virgilio A, Rizzo MI, Tombolini M, Gallo A, Fusconi M, Ruoppolo G, Pagliuca G, Martellucci S, de Vincentiis M. Kawasaki disease: an evolving paradigm. *Autoimmun Rev* 2015; 14:703-9; PMID:25882057; <http://dx.doi.org/10.1016/j.autrev.2015.04.002>
- [3] Jamieson N, Singh-Grewal D. Kawasaki disease: A clinician's update. *Int J Pediatr* 2013; 2013:645391; PMID:24282419; <http://dx.doi.org/10.1155/2013/645391>
- [4] Bonetto C, Trotta F, Felicetti P, Alarcón GS, Santuccio C, Bachtiar NS, Brauchli Pernus Y, Chandler R, Girolomoni G, Hadden RD, et al. Vasculitis as an adverse event following immunization - Systematic literature review. *Vaccine* 2015 [Epub ahead of print]; pii: S0264-410X(15)01292-X; PMID:26398442; <http://dx.doi.org/10.1016/j.vaccine.2015.09.026>
- [5] Gorman KM, Gavin PJ, Capra L. Bacillus calmette-guérin scar erythema: "Haloing" the diagnosis in Kawasaki disease. *J Pediatr* 2015; 167:774; PMID:26205182; <http://dx.doi.org/10.1016/j.jpeds.2015.06.043>
- [6] Uda K, Hataya H. Ulceration at bacillus calmette-guérin inoculation site in a patient with Kawasaki disease. *J Pediatr* 2015; 167(5):1167-7.e1; PMID:26342720; <http://dx.doi.org/10.1016/j.jpeds.2015.08.018>
- [7] Sethuraman G, Ramesh V. Cutaneous tuberculosis in children. *Pediatr Dermatol* 2013; 30:7-16; PMID:23173930; <http://dx.doi.org/10.1111/j.1525-1470.2012.01794.x>
- [8] Muto J, Kuroda K, Tajima S. Papular tuberculides post-BCG vaccination: case report and review of the literature in Japan. *Clin Exp Dermatol* 2006; 31:611-2; PMID:16716184; <http://dx.doi.org/10.1111/j.1365-2230.2006.02083.x>
- [9] Takada T, Yamashita T, Sato M, Kawakami Y, Tominaga A, Ono I, Jimbow M, Tsutsumi H, Jimbow K. Papulonecrotic tuberculid-like eruptions after Bacille Calmette-Guerin vaccination. *J Dermatol* 2007; 34:183-8; PMID:17291299; <http://dx.doi.org/10.1111/j.1346-8138.2007.00246.x>
- [10] Ishigaki M, Oishi Y, Asou S. Two cases of Papulonecrotic tuberculid after Bacille Calmette-Guerin (BCG) vaccination. *Shonika Rinsho* 2012; 65:989-96; (Japanese)
- [11] Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette-Guérin inoculation site. *Pediatr Infect Dis J* 2010; 29:430-3; PMID:20032807; <http://dx.doi.org/10.1097/INF.0b013e3181cacede>
- [12] Sireci G, Dieli F, Salerno A. T cells recognize an immunodominant epitope of heat shock protein 65 in Kawasaki disease. *Mol Med* 2000; 6:581-90; PMID:10997339
- [13] Miron D, Fink D, Hashkes PJ. Kawasaki disease in an infant following immunisation with hepatitis B vaccine. *Clin Rheumatol* 2003; 22:461-3; PMID:14677029; <http://dx.doi.org/10.1007/s10067-003-0785-3>
- [14] Shimada S, Watanabe T, Sato S. A Patient with Kawasaki Disease Following Influenza Vaccinations. *Pediatr Infect Dis J* 2015; 34:913; PMID:26376188; <http://dx.doi.org/10.1097/INF.0000000000000713>
- [15] Seo JH, Yu JJ, Ko HK, Choi HS, Kim YH, Ko JK. Diagnosis of incomplete kawasaki disease in infants based on an inflammation at the bacille calmette-guérin inoculation site. *Korean Circ J* 2012; 42:823-9; PMID:23323120; <http://dx.doi.org/10.4070/kcj.2012.42.12.823>
- [16] Lai CC, Lee PC, Wang CC, Hwang BT, Meng CC, Tsai MC. Reaction at the bacillus Calmette-Guérin inoculation site in patients with Kawasaki disease. *Pediatr Neonatol* 2013; 54:43-8; PMID:23445742; <http://dx.doi.org/10.1016/j.pedneo.2012.10.003>
- [17] Yin S, Liubao P, Chongqing T, Xiaomin W. The first case of Kawasaki disease in a 20-month old baby following immunization with rotavirus vaccine and hepatitis A vaccine in China: A case report. *Hum Vaccin Immunother* 2015; 11:2740-3; PMID:26158590; <http://dx.doi.org/10.1080/21645515.2015.1050571>
- [18] Hua W, Izurieta HS, Slade B, Belay ED, Haber P, Tiernan R, Woo EJ, Iskander J, Braun MM, Ball R. Kawasaki disease after vaccination: reports to the vaccine adverse event reporting system 1990–2007. *Pediatr Infect Dis J* 2009; 28:943-7; PMID:19755926; <http://dx.doi.org/10.1097/INF.0b013e3181a66471>
- [19] Abrams JY, Weintraub ES, Baggs JM, McCarthy NL, Schonberger LB, Lee GM, Klein NP, Belongia EA, Jackson ML, Naleway AL, et al. Childhood vaccines and Kawasaki disease, Vaccine Safety Datalink,

- 1996–2006. *Vaccine* 2015; 33:382-7; PMID:25444786; <http://dx.doi.org/10.1016/j.vaccine.2014.10.044>
- [20] Park YM, Kang H, Cho SH, Cho BK. Lichen scrofulosorum-like eruption localized to multipuncture BCG vaccination site. *J Am Acad Dermatol* 1999; 41:262-4; PMID:10426899; [http://dx.doi.org/10.1016/S0190-9622\(99\)70059-9](http://dx.doi.org/10.1016/S0190-9622(99)70059-9)
- [21] Figueiredo A, Poiars-Baptista A, Branco M, da Mota HC. Papular tuberculids post-BCG vaccination. *Int J Dermatol* 1987; 26:291-4; PMID:3610434; <http://dx.doi.org/10.1111/j.1365-4362.1987.tb00191.x>
- [22] Evans RG, Warner J. Lichen scrofulosorum following B.C.G. *Arch Dis Child* 1967; 42:448; PMID:4951645; <http://dx.doi.org/10.1136/adsc.42.224.448>
- [23] Zaïem A, El Ferjani S, Lakhoua G, Sahnoun R, Badri T, Kastalli S, Daghfous R, Lakhal M, El Aidli S. Probable disseminated BCG infection in a 10-month-old child after BCG vaccination. *Hum Vaccin Immunother* 2014; 10:2081-2; PMID:25424819; <http://dx.doi.org/10.4161/hv.28913>
- [24] Karte K, Wollina U. Postvaccination inflammatory papules of the skin—think of Bacille Calmette-Guérin (BCG). *Pediatr Dermatol* 1998; 15:73-4; PMID:9496818; <http://dx.doi.org/10.1046/j.1525-1470.1998.1998015073.x>
- [25] Atasoy M, Aliğaoglu C, Erdem T, Ozdemir S, Aktaş A. Scrofuloderma following BCG vaccination. *Pediatr Dermatol* 2005; 22:179-80; PMID:15804315; <http://dx.doi.org/10.1111/j.1525-1470.2005.22222.x>