Borderline Tuberculoid Leprosy following BCG Vaccination. A Case Report[1]

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We describe a case of leprosy in a child following vaccination with Bacillus Calmette-Guerin (BCG). Our finding confirms observations made more than 20 years ago ([2,5,9]) and illustrates a concept of the leprosy spectrum which has important implications for the design and interpretation of a leprosy vaccine trial ([12]).

CASE REPORT

A four year-old boy was brought to the leprosy clinic by his mother, aged 33 years, in December 1979 because she had noticed the development of hypopigmented patches starting six months previously. There are three older boys in the family, ages 12, 11, and 7 years, who are free of leprosy. Both the mother and the father are registered patients at the All Africa Leprosy and Rehabilitation Training Centre (ALERT) and live in the village nearby. The mother has been treated irregularly for leprosy (probably borderline tuberculoid) beginning 20 years ago. Her record does not indicate any skin smears positive for acid-fast bacilli (AFB), but following the birth of her third child she developed severe clawing of both hands. Her husband has had lepromatous leprosy since the age of 12 years and has been treated for the past 25 years.

The boy presented with a hypopigmented macule (5.2 × 7.5 cm) on the upper right arm surrounding a vaccination scar which remained pigmented (The Figure). There were four small satellite lesions. The skin in the lesion was dry, and sensory testing showed partial loss of sensation. A smaller lesion (2.1 × 3.0 cm) with one satellite was present on the chin. In comparison to the arm lesion, the loss of pigment from the chin lesion was less intense, the edge of the lesion was slightly raised, and the surface of the skin was moist. There were no enlarged peripheral nerves.

The mother reported that the hypopigmented arm lesion started to appear 2 weeks after the boy had been vaccinated about 6 months previously. The lesion began above the vaccination site and subsequently spread down and around both sides of it. The lesion on the chin did not start to appear until 2 months after the arm lesion became evident. A check with the Ministry of Health, Addis Ababa, revealed that BCG vaccine (Glaxo) was used at the reported time in the area where the boy lives as a part of their tuberculosis control program.

MATERIALS AND METHODS

Skin smears. Slit-skin smears for AFB were performed as described previously ([1]).

Histology. Histological examination was done on hematoxylin-eosin and on TRIFF-stained sections of a 4 mm punch biopsy of lesional skin ([10]).

Lymphocyte transformation test. The lymphocyte transformation test was performed as previously described ([13]) except that each culture contained 100,000 cells. The *M. leprae* used for lymphocyte stimulation was a preparation (batch AB 21) of armadillo-grown bacilli obtained through the IMMLEP program of the Special Programme for Research and Training in Tropical Diseases of the World Health Organization (WHO). The bacilli had been purified according to the procedure of Draper ([14]). Other antigens used were purified tuberculin, PPD (Statens Seruminstitut, Copenhagen), BCG (Glaxo), streptokinase-streptodornase, SKSD (Varidase®,

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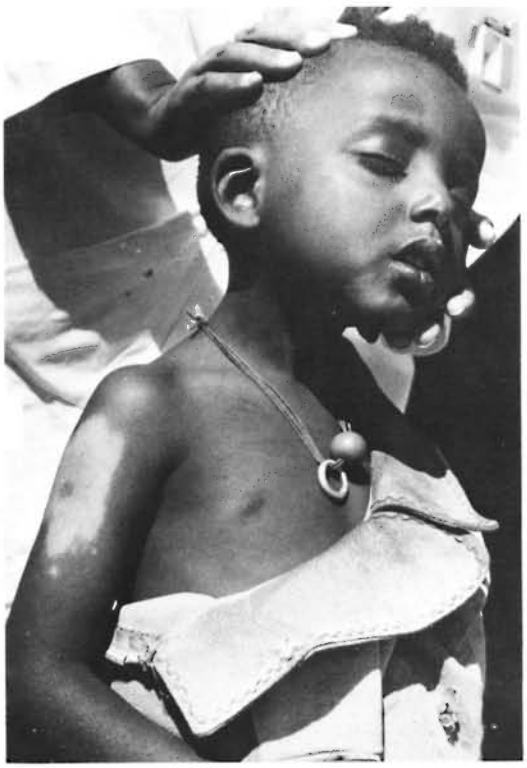

THE FIGURE. Four year-old male patient with borderline tuberculoid leprosy following BCG vaccination.

Lederle), and mumps skin test antigen (Eli Lilly).

Statistical analysis. Significance of differences between means was determined by the Student's *t* test.

RESULTS

Skin smears from six sites including the lesions showed no acid-fast bacilli. A punch biopsy was taken from the lower edge of the arm lesion. Sections stained with hematoxylin-eosin showed the epidermis somewhat flattened over several epithelioid cell granulomas in the upper dermis. The subepidermal zone showed chronic inflammatory cell infiltrations around a hair follicle, a sweat gland, and an arrector pili muscle. Some giant cells were present. No bacilli could be found on TRIFF-stained sections.

The results of the lymphocyte transformation test are shown in the Table. The responses to BCG and to *M. leprae* did not differ significantly.

THE TABLE. *Responses in the lymphocyte transformation test to mycobacterial antigens, SKSD, and mumps antigen.*

Antigen	^{3}H-thymidine incorporation (mean cpm ± S.D.)	Stimulation index
Control	626 ± 148	—
M. leprae, 3×10^7/ml	10,354 ± 1754	16.5
BCG, 3×10^7/ml	15,179 ± 3029	24.2
PPD, 1,0 μg/ml	12,747 ± 3609	20.4
SKSD, 250 U/ml	7856 ± 1483	12.6
Mumps, 1:100	6685 ± 2125	10.7

A diagnosis of borderline tuberculoid (BT) leprosy was made, and the boy was started on dapsone (DDS), 25 mg daily.

DISCUSSION

This case reported to the clinic within 6 months of BCG vaccination because the mother, a leprosy patient herself, was concerned about the progression of the skin lesions. She was aware of the precise relationship between the vaccination and the first appearance of the arm lesion, but she did not regard the vaccination as the cause of the leprosy. The boy presented a fairly typical clinical and histological picture of BT leprosy except for the unusual relationship of the arm lesion to the vaccination site. In 6 months of observation since he was first seen in the clinic, his condition has remained entirely stable. The data from the lymphocyte transformation test are consistent with the diagnosis of BT leprosy in that the response to *M. leprae* was not significantly different from the responses to BCG and PPD. This finding in a boy actively immunized with BCG only 6 months previously is consistent with the presence of a tuberculoid leprosy infection.

The evidence that the BCG vaccination was a factor in precipitating the leprosy rests solely on the temporal relationship between the two. Certainly, the appearance of the hypopigmented arm lesion only 2 weeks after the vaccination precludes the possibility that the leprosy bacilli entered the skin at the time of the vaccination. It is noteworthy that the arm lesion started above, not in, the vaccination site and spread down and around it. These facts,

and the appearance of a second lesion on the chin, serve to differentiate this case from leprosy lesions which can occur at sites of trauma ([7]). Our interpretation is that boosting of the delayed-type hypersensitivity and/or cell-mediated immunity (CMI) to mycobacterial antigens by the intradermal BCG inoculation precipitated clinical leprosy in an individual with subclinical disease. The limited size and distribution of the lesions without enlarged peripheral nerves suggest that the infection was in an early stage. If there had been no immunologic intervention, it seems possible that this case could have proceeded through a latent period without overt clinical symptoms toward multibacillary leprosy.

There have been reports from three independent groups concerning the appearance of tuberculoid leprosy in children within a few weeks to a few months following BCG vaccination ([2,5,9]). These observations were difficult to reconcile with views prevailing at the time, and the significance of these early reports seems to have been largely overlooked. The case presented in this paper serves to emphasize that BT leprosy can occur in close association with BCG vaccination and, although causality can never be proved, the conclusion that the BCG vaccination was the principal precipitating factor seems reasonable.

If the spectrum of clinical leprosy can be attributed to a succession of three phases of suppression as has been suggested ([12]), then this case can be viewed as the interruption of a Phase I (primary) suppression by an intradermal vaccine boosting CMI to antigens of *M. leprae*. Suppression could be maintained by central lymphon stimulation with bacilli leaking into the circulation from an intraneural primary focus of infection ([11]). Presumably the vaccine, delivered to the peripheral lymphon compartment as is required for effective CMI ([6]), tips the balance in favor of immunity.

This case also illustrates the difficulties which this phenomenon presents for controlled trials of anti-leprosy vaccines. If this child had been administered an anti-leprosy vaccine as part of a trial at the time he received the BCG, he would have been recorded as a leprosy case in the vaccinated group and thus as a "failure" of the vaccine. If, on the other hand, this boy had been in the non-vaccinated control group, his leprosy might have remained subclinical throughout the trial period, in which case he would not have been recorded as a leprosy case at all. Precipitation of inapparent leprosy infections as "closed" cases before they can become infectious is desirable for controlling the spread of leprosy. However, this phenomenon will actually tend to increase the incidence of leprosy in the vaccinated group compared to the control group.

This phenomenon should be identifiable not only in the rare individual case due to fortuitous circumstances but also in large-scale trials of anti-leprosy vaccines. In this regard it is of interest that in the trial of BCG carried out by WHO in Burma, there was an unexplained excess of leprosy cases in the vaccinated group compared to the control group at the first annual followup ([3]). At the second annual followup the incidence of leprosy was lower in the vaccinated group than in the control group. This difference approaches statistical significance ($\chi^2 = 2.83$, $p < 0.10$).

This phenomenon could be even more important in a trial of a specific vaccine derived from *M. leprae* if individuals who respond weakly or not at all to a "PPD" of *M. leprae*, e.g., Convit's soluble protein antigen (SPA) ([4]) or Harboe and Closs' antigen 7 of *M. leprae* ([8]), were to be selected for inclusion in the vaccine trial. This procedure may tend to select for those very individuals in the population who are already in Phase I suppression ([12]) and who would be incubating a subclinical leprosy infection. Some of these, when vaccinated, would likely be cured without the appearance of clinical symptoms. But in others, borderline leprosy, ranging from borderline tuberculoid to borderline lepromatous, would appear soon after vaccination. On the other hand, some of these who are in the unvaccinated control group may remain undetected for the duration of the trial.

Clearly, careful consideration must be given to the time interval between vaccination and the appearance of leprosy lesions as well as to any difference in the types of leprosy occurring in the vaccinated and control groups. The trial period should be longer than the average incubation pe-

riod of lepromatous leprosy. From our limited knowledge, 5 years would seem to be a minimum trial period, while a 10 year trial period would provide additional data on leprosy infections acquired after, rather than before, the time of vaccination.

SUMMARY

Borderline tuberculoid leprosy was diagnosed clinically and histologically in a four year-old boy about 6 months after intradermal vaccination with BCG. His mother reported that a lesion began to appear above the vaccination site on the arm 2 weeks after the vaccination, and a second lesion appeared on the chin 2 months later. Responses in the lymphocyte transformation test to sonicated *Mycobacterium leprae*, BCG, and to PPD were consistent with a tuberculoid leprosy infection.

Precipitation of BT leprosy by intradermal BCG infection may possibly represent the overcoming of a phase of primary suppression in an individual who might otherwise have progressed toward lepromatous leprosy. The implications of this hypothesis for the planning of a controlled trial of an anti-leprosy vaccine are discussed.

RESUMEN

Se diagnosticó clínica e histológicamente un caso de lepra tuberculoide-intermedia (borderline tuberculoid, BT) en un niño de 4 años, aproximadamente 6 meses después de la vacunación intradérmica con BCG. La madre informó que la lesión empezó a aparecer, arriba del sitio de vacunación en el brazo, 2 semanas después de la inoculación y que una segunda lesión apareció en la barba dos meses después. Los resultados de la prueba de la transformación de linfocitos con sonicados de *Mycobacterium leprae*, BCG, y con PPD, fueron consistentes con una infección leprosa del tipo tuberculoide.

El desencadenamiento de la lepra, BT, por la vacunación intradérmica con BCG puede, posiblemente, significar la emergencia de una fase de supresión primaria en un individuo que pudiera, en otras circunstancias, permitir el desarrollo del tipo lepromatoso de la enfermedad. Se discuten aquí, las implicaciones de esta hipótesis en el caso de planearse un ensayo controlado con una vacuna anti-lepra.

RÉSUMÉ

Une lèpre tuberculoïde de type borderline a été diagnostiquée cliniquement et histologiquement chez un garçon âgé de 4 ans, à peu près six mois après une vaccination par le BCG par voie intradermique. La mère de l'enfant a signalé que la lésion avait commencé à apparaître au-dessus de l'endroit de la vaccination, au niveau du bras, 2 semaines après cette vaccination, et qu'une seconde lésion était apparue sur le menton 2 mois plus tard. Les réponses obtenues lors de l'épreuve de transformation lymphocytaire à l'égard de bacilles de la lèpre tués par ultrasons, de BCG et de PPD, étaient compatibles avec une infection de lèpre de type tuberculoïde.

L'éclosion d'une lèpre de type tuberculoïde borderline, à la suite d'une infection intradermique par le BCG, pourrait éventuellement représenter le dépassement d'une phase de supression initiale chez un individu qui autrement aurait progressé vers la lèpre lépromateuse. Les implications d'une telle hypothèse pour la planification d'un essai contrôlé de vaccin contre la lèpre, sont discutées.

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