Disseminated BCG infection in a child with chronic granulomatous disease

A case report

P. A. G. SMITH, D. F. WITTENBERG

Summary

A patient suffering from chronic granulomatous disease (then undiagnosed) developed progressive BCG infection from the age of 4 months. At about the age of 10 months his parents instituted legal action against the State on the grounds that their consent for BCG vaccination had been given when they were uninformed; approximately 4 months later the underlying immune defect was established.

Complications of BCG vaccination are rare. The various factors that may be involved in their aetiology are outlined, and the association of chronic granulomatous disease and progressive BCG infection is briefly discussed.

Complications of BCG vaccination are rare. They may be expected to occur in 1/100,000 - 800,000 cases and include anaphylaxis, local abscesses, various skin manifestations and dissemination to lymph nodes, liver, lung, eye and bone. Approximately 35 deaths from disseminated BCG infection have been reported. The fault may lie with the vaccine, the method of administration or, most commonly, with a defect of host defence mechanisms. In some cases the exact defect could not be elucidated, but the association of disseminated BCG infection with combined immunodeficiency and chronic granulomatous disease (CGD) is well described. The first case of disseminated BCG infection in association with CGD was described by Esterly in 1971. At least 7 confirmed cases have subsequently been reported. A number of patients with CGD have received antituberculosis therapy for presumed BCG infection without confirmation of the presence of acid-fast bacilli.

Both CGD and disseminated BCG infection may present with lymphadenopathy, hepatosplenomegaly and hilar lymphadenopathy, and the histological appearances are similar. The exact diagnosis therefore depends on the isolation of acid-fast bacilli or a response to specific therapy.

We report the case of a 14-month-old boy who had received chemotherapy for proven disseminated BCG infection before the diagnosis of CGD was established.

Case report

This White male infant was the first child of non-consanguineous parents. There were no problems during the neonatal period. A standard dose of 0.1 ml BCG vaccine was administered over the insertion of the right deltoid muscle on the 3rd day with no local complications. At the age of 3 weeks blood and pus were noted in his stools. No cause was found on culture and sigmoidoscopy and the problem settled spontaneously. From 4 months of age he developed progressive lymphadenopathy in the right axilla. A chest radiograph revealed widening of the superior mediastinum, this being compatible with mediastinal adenopathy. Aspiration of an axillary lymph node revealed acid-fast bacilli, confirmed on culture to be mycobacteria. Appropriate chemotherapy was selected in accordance with results of sensitivity testing. This consisted of isoniazid (INH), rifampicin, ethambutol and pyrazinamide. However, the lymph nodes continued to enlarge. At 6 months of age a right axillary lymph node clearance was performed under general anaesthesia. On examination of a histological section the normal lymphoid tissue was seen to be totally replaced by granulation tissue with areas of central caseation and Langerhans' giant cells (Fig. 1). Acid-fast bacilli were demonstrated on Ziehl-Neelsen staining.

Department of Paediatrics, Addington Hospital and University of Natal, Durban

D. F. WITTENBERG, M.B. CH.B., F.C.P. (S.A.)
An enlarged left cervical lymph node was subsequently removed. No acid-fast bacilli were demonstrated but Klebsiella species were isolated on culture. At 7 months of age the infant’s chest radiograph appeared to be normal. No further adenopathy had developed, and the pyrexia and ethambutol were discontinued. From 10 months of age onwards the patient experienced recurrent episodes of pneumonia. These involved differing pulmonary segments as seen on radiography and on each occasion responded to antibiotic treatment. By this time the patient’s parents had instituted legal proceedings against the State, claiming compensation on the grounds that their consent for BCG vaccination had been given when they were uninformed.

An immune defect involving T- and B-cell immunity was ruled out by the following measurements: the peripheral white cell count was 28.9 x 10^9/L and the lymphocyte count was 14.6 x 10^9/L (65% T cells and 35% B cells). Lymphocyte transformation, as measured by the response to phytohaemagglutinin stimulation, was normal. The immunoglobulin levels were as follows: IgA 2200 mg/dL, IgM 1870 mg/dL and IgG 9.87 g/L. The complement C3 level was 148 mg/dL. No auto-antibodies were detected.

When the patient was referred to the Addington Children’s Hospital at the age of 14 months (on account of yet another episode of pneumonia) he weighed 9.4 kg (10th Boston percentile) and his height was 75 cm (10th percentile). Apart from right middle lobe pneumonia he had a 4 cm firm hepatosplenomegaly but no lymphadenopathy. Although no aetiological organism was isolated, he responded to treatment with ampicillin and gentamicin, but no lymphadenopathy. Although no aetiological organism was isolated, he responded to treatment with ampicillin and gentamicin, but no lymphadenopathy. Although no aetiological organism was isolated, he responded to treatment with ampicillin and gentamicin, but no lymphadenopathy. Although no aetiological organism was isolated, he responded to treatment with ampicillin and gentamicin, but no lymphadenopathy. Although no aetiological organism was isolated, he responded to treatment with ampicillin and gentamicin, but no lymphadenopathy.

A diagnosis of CGD was made and co-trimoxazole and INH prophylaxis was started. Despite this, the patient suffered further attacks of pneumonia and peri-anal abscesses. Staphylococcus aureus was isolated on culture. A nitroblue tetrazolium test (NBT) showed no positive cells, even after in vitro stimulation. A neutrophil bactericidal test showed no evidence of bactericidal activity. Similar tests on the parents showed his father to have normal responses and his mother to have intermediate results; the yeast phagocytosis assay showed phagocytosis in both parents to be normal.

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In normal individuals phagocytosis of bacteria involves a burst of metabolic activity within the neutrophils, resulting in the production of superoxide, hydrogen peroxide and hydrogen radicals. These, along with lysosomal myeloperoxidase and halide ions, are responsible for the intracellular killing of ingested bacteria and fungi. In CGD the neutrophils appear to have defective membrane-bound oxidase enzyme, with the result that phagocytosis does not stimulate intracellular metabolism and therefore no reactive superoxide or hydrogen peroxide radicals are formed. Unless the ingested organism is catalase-negative and therefore unable to degrade its own endogenously produced hydrogen peroxide, it will survive within the cell. The blood-borne dissemination of such macrophages containing viable organisms throughout the reticuloendothelial system and to many organs then results in the clinical disease.

The NBT, which detects the presence of superoxide anion, characteristically gives zero readings in cases of CGD,2 but could be reduced in instances of defective phagocytosis. In healthy, normal mononuclear cells the NBT score is 80% or more.8 In undamaged cells of bacterial sepsis and tuberculosis it is high,9 reflecting stimulation of the microbicidal mechanisms within the neutrophils. In our patient the NBT score was zero although he was suffering from bacterial sepsis, and it remained zero when repeated after his neutrophils had been incubated with endotoxin to stimulate metabolic activity.

The inability of his cells to kill bacteria was confirmed by the negative bactericidal test, which assesses the neutrophils’ capacity to kill intracellular (phagocytosed) staphylococci. Unfortunately, yeast phagocytosis was not assayed before his death; an abnormality of phagocytosis was therefore not excluded. In conjunction with the low NBT score, the negative bactericidal assay and the normal phagocytosis assay found upon testing his mother, a confident diagnosis of CGD with probably X-linked recessive inheritance could be made.

Inoculation with BCG seeks to provide immunity against tuberculosis similar to that produced by a primary infection. Immunity to mycobacteria involves primarily cell-mediated immunity. Through the production of lymphokines sensitized T cells mediate the ingestion and killing of mycobacteria by activated monocytes and tissue macrophages.10 In CGD monocytes and tissue macrophages show the same defect of intracellular killing as is present in the neutrophils.11 Since BCG is a catalase-positive organism it remains viable within these cells, and can be disseminated and produce clinical disease. Our patient had disseminated BCG infection and acid-fast bacilli were found in lymph nodes. He had hilar adenopathy which responded to antituberculosis chemotherapy. Chemotherapy for disseminated BCG infection may be ineffective or difficult and prolonged in cases of CGD. Esterly et al.5 and Keller’s12 patients died despite intensive antituberculosis therapy. The 2 patients described by Verronen3 responded to treatment comprising INH, para-aminosalicylic acid, streptomycin, ethambutol and pyrazinamide. The choice of drugs should include intracellularly active agents such as INH and rifampicin12 as well as an agent which could stimulate the T-lymphocyte system, as has been given for a prolonged period. Despite the inclusion of these two drugs in our patient’s treatment, his auxiliary lymphadenopathy progressed until the lymph nodes were removed surgically. Thereafter no new BCG adenopathy developed. The mediastinal adenopathy receded as seen on radiography. The tuberculin test was negative when the diagnosis of CGD was made. These facts suggest that the disseminated BCG infection had responded to treatment. The subsequent course of our patient is compatible with the natural history of CGD. We do not believe disseminated BCG infection to have been a significant factor in his eventual demise.

The publicity that this case received in local medical circles, coupled with the threat of legal action by the parents, led to questioning of the status of routine BCG vaccination of White neonates (before the underlying defect was diagnosed). Disseminated BCG infection is almost always due to an underlying immune defect. The practitioner must therefore conduct a thorough search for such a defect in order to provide appropriate treatment and genetic counselling and to avoid litigation.

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REFERENCES