Tr. J. of Medical Sciences
29 (1999) 285-289

Mustafa HACIMUSTAFAOĞLU[1]
Mehmet OKAN[1]
Ömer YERCİ[2]
Suna GEDİKOĞLU[3]
İrfan KIRIŞTIOĞLU[1]
İbrahim ILDIRIM[1]

Generalized BCG Lymphadenitis in an Infant: Diagnostic Dilemma With Lepromatous Leprosy and Gaucher Disease on Fine Needle Aspiration

Received: May 26, 1997

Department of [1]Pediatrics, [2]Pathology, [3]Microbiology, Faculty of Medicine, Uludağ University, Bursa-Turkey

Abstract: A two-year old male infant with generalized BCG lymphadenitis is presented. There was no obvious immunodeficiency disorder detected in the patient. BCG vaccine had been given at two months of age, and the lymphadenopathy developed at 21 months of age. Fine needle aspiration biopsy of the lymph node on Giemsa stain revealed macrophages very similar to Gaucher cells. These cells also resembled macrophages seen in lepromatous leprosy. They were engorged with acid fast bacilli and had streaked or wrinkled cytoplasm. Mycobacterium bovis was cultured from the lymph nodes and the patients improved with antituberculous therapy.

Key Words: BCG, Gaucher, leprosy, lymphadenitis.

Introduction

Vaccination with Bacillus Calmette-Guerin (BCG) strain of mycobacterium is used throughout the world, especially in developing countries to reduce the risks of natural tuberculous infection.

BCG vaccine is considered to be one of the safest vacines (1) with self-limited regional lymphadenophathy being the most common complication. It has been suggested that vaccination at three months of age may reduce the prevalence of this complication (2). Although, the frequency of BCG-associated regional lymphadenitis is 0.5-16.6%, generalized lymphadenitis is a very rare complication of BCG vaccination (2-4). The prevalence rate of disseminated BCG infection described as at least two areas beyond the inoculation site, has been estimated at 0.59 cases per 1 million vaccinated children most of them with lymphadenitis (5). However, serious BCG infections may occur, in individuals with immunodeficiency conditions. There are also reports of apparently normal individuals (approximately half of the cases) with disseminated and even fatal infections (5-7). However, in most of these patients, it is likely that an underlying immunological defect may have been undiagnosed (8-10). It is reported that fine needle aspiration biopsy in patients with generalized lymphadenitis due to BCG vaccine may show Gaucher like cells (3).

In this paper, we presented a two-year-old boy with generalized BCG lymphadenitis whose fine needle aspiration biopsy showed Gaucher like cells as well as macrophages resembling those seen in patients with lepramatous leprosy showed BCG histiocytosis was demonstrated by excisional biopsy. Cultures from both aspiration and excisional biopsy material material revealed Mycobacterium bovis.

Case Report

A two-year-old male infant was admitted to our clinic with the complaint of generalized lympadenitis. His perinatal history was unremarkable and he had a birth weight of 3500 g. Routine BCG vaccination was done at two months of age in addition to all other routine vaccinations which were carried out systematically. At eight months of age, left axillary lymphadenopathy (1x2 cm node) was detected which was thought to be due to BCG vaccination, and 10 mg/kg/d Isoniazid (INH) was recommended for a six month period. The regional lymphadenopathy began to regress in one month (1x1.5 cm). However, his parents discontinued treatment after that time. Approximately at 21 months of age, generalized (bilateral, axillary, inguinal, and cervical) lymphadenopathy developed. There was no familial history of tuberculosis and no history of immunodeficiency, oral candida infection, or recurrent

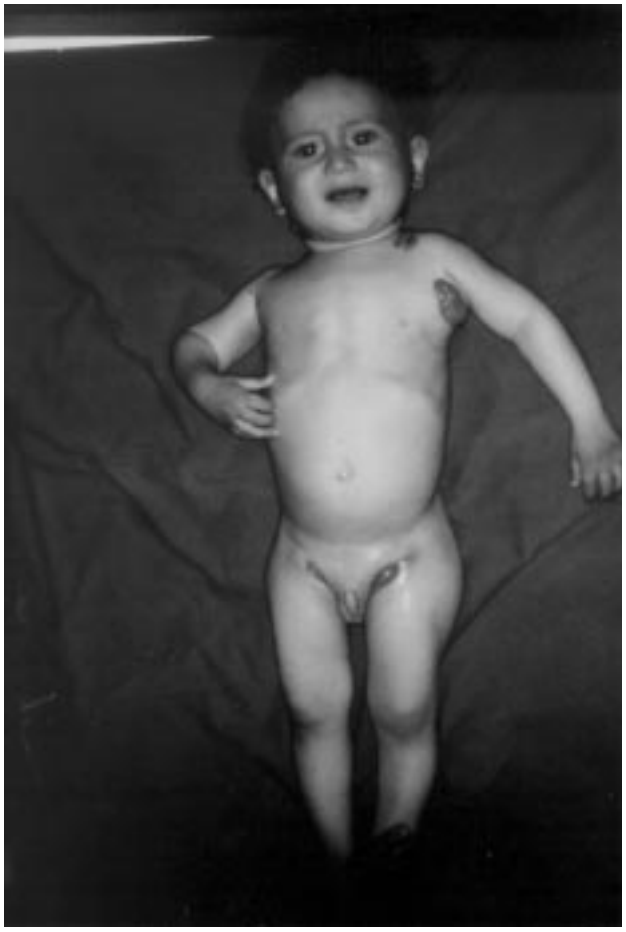

Figure 1. The patient has generalized, bilateral, cervical, axillary, and inguinal lymphadenitis at admission.

infections. The patient was breastfed until 20 months of age. He had neonatal transient diaper dermatitis probably due to candida.

At admission, the physical examination revealed that his axillary temperature was 36.3°C, weight 9850 g (3-10 percentile), length 80 cm (3-10 percentile), and head circumference 47 cm (25 percentile). His oral hygiene was poor and there were numerous cavities in the teeth. There were a number of bilateral cervical, axillary and inguinal, fistulized and pruritic lymphadenopathy up to 8x7 cm in diameter with keloid scars (Figure 1). The skin overlying the lymph nodes was broken down, red and oozing. Signs of rickets (Harrison groove, caput quadratum and widened epiphyses) were also present. There was a BCG vaccine scar, 0.2x0.7 cm in diameter, on his left shoulder. The liver was palpable 2 cm below the right costal margin. There was no splenomegaly. The rest of the physical examination findings and neurodevelopmental status were in normal range.

The laboratory studies revealed a normal complete bood count, electrolytes, renal and hepatic function tests. The serological tests for HIV, cytogmegalovirus and Epstein-Barr virus were negative. The immunoglobulin G, A and M concentrations, lymphocyte subgroups, and nitrobluetetrazolium (NBT) tests were in normal range. Bone marrow findings were normal. The intradermal skin test with 5 TU PPD and candida were negative, but there was a 3x4 mm induration in response to tetanus. Chest radiography revealed no specific lesions and X-rays of the extremities were compatible with rickets. Gram stain of the material from the surfaces and fistulae orifices showed Gram positive cocci, and Staphylococcus aureus

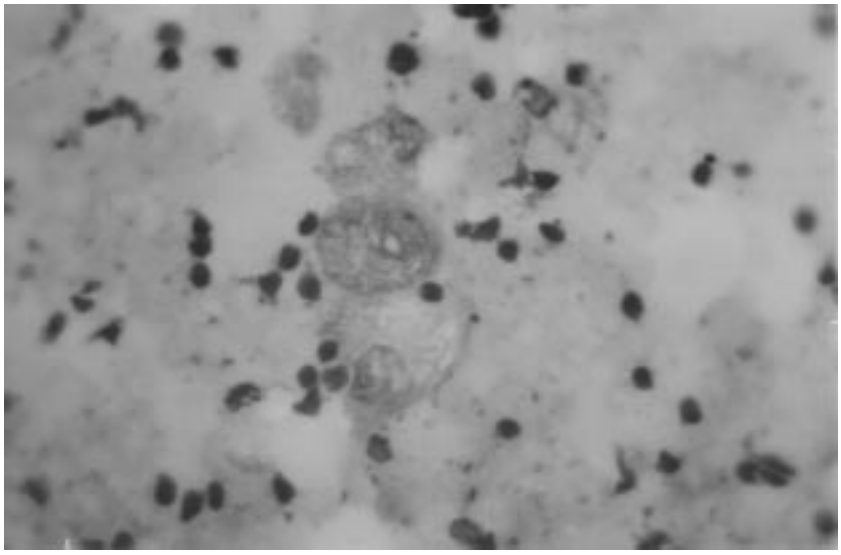

Figure 2. Fine needle aspiration biopsy showed Gaucher like-cells on Giemsa stain (x800)

(sensitive to penicillin) was recovered in culture. Fine needle aspiration biopsy from left axillary lymph node was reported as Gaucher cells on Giemsa stain (Figure 2). Later, special staining with Ziehl-Nielsen for acid-fast bacilli revealed abundant bacilli in both inside and outside of the macrophages. Periodic Acid Schiff (PAS) staining was also positive. These cells also resembled the cells seen in lepromatous leprosy. Warthin-Starry (pH:4.0) staining was negative for spirochetes. Results of excisional biopsies of the affected nodes (right axillary lymh nodes) revealed the histologic appearance of BCG histiocytosis. Cultures in Lowenstein-Jensen media of the fine needle aspiration and excisional biopsy specimens gave positive results for M. bovis (BCG) about two months later. Identification of isolates as BCG was confirmed by a negative niacin test and negative nitrate reduction test, as well as catalase production at room temperature but not at 68°C. Antimicrobial susceptibility test could not be performed. TNF and the other cytokines or cytokine reseptor levels could not be tested.

The patient was given ampicillin for a two-week period for superinfection. After the positive histologic results were obtained, antituberculous therapy with INH (10 mg/kg/d), rifampicin (15 mg/kg/d) and pyrazinamid (30 mg/kg/d) were given for two months along with streptomycin (20 mg/kg/d) during the first month of treatment. After two months, the therapy was continued as rifampicin plus INH for 9 months.

After two months of therapy, skin tests were performed again with similar results (negative for PPD and candida, and borderline at 4x6 mm induration to tetanus). At this time, the patient began to improve. However, the diameters of the involved nodes were up to 4x5 cm with keloid scars. At six months of therapy, the maximal diameter of the nodes was 2x1.5 cm with minimal keloid scars.

Discussion

Generalized lymphadenapthy is an unusual complication of BCG vaccination and only a few cases have been reported (3, 4). In our patient, there was no apparent serious immunological defect (except for tuberculin anergy in spite of BCG vaccination, and negative candida skin test). Although some of the immunological studies especially regarding the cellular immunity such as lymphocye transformation tests and cytokines and cytokine receptors could not be performed, other general cellular and humoral immunological tests were in the normal range. There were neither significant symptoms attributed to recurrent infectious diseases nor physical/developmental retardation before the development of the generalized lymphadenitis. However, it is possible that there may have been an underlying, undiagnosed, subclinical immunological defect. It is reported that disseminated BCG infections may occure in a previously healthy child with complete lack of skin test reactivity to PPD and the other antigen tests such as candida or mump. Severe disseminated BCG infection may cause transient T cell depression and abnormal monocytic histochemical reactions (11). Disseminated BCG infection involving several lymph nodes may be seen in children with chronic granulomatous disease (11, 12), but in our patient, the clinical history and NBT test results were not compatible with this condition. Monocytes and macrophages play an important role in efferent arm of the immune response to infections with mycobacteria. Sustained suppression of antibody dependent cellular cytotoxicity lasts for approximately nine months after clinical remission (3), and a defect of monocyte candidacidal activity but normal lymphocyte function (14) in disseminated nontuberculosis mycobacteriosis have been observed. In an experimental animal study, mice given large doses of BCG have developed skin test anergy and depressed T cell responses with increased splenic suppressor T cells which might hamper host defense mechanisms during active infection (15). It has been suggested that disseminated BCG infection in patients without any well-defined immunodeficiency condition, probably results from an as yet unknown genetically determined immunodeficiency condition that affects the killing of intracellular bacteria such as BCG (5, 16).

There may be some differences in terms of potency and adverse effect among the various BCG vaccine products. BCG vaccines in Turkey are delivered by the Health Ministry. The fact that there has been no vaccine-related infection due to this strain of vaccine reported so far made this probability unlikely.

Before the culture results were available, it was thought that another strain of mycobacterium especially acquired by oral-gastrointestinal route might also cause this clinical picture. Both culture results and normal abdominal ultrasound findings without any significant lymphadenopathy or thickened intestinal wall made this possibility unlikely.

In our patient, although there were no findings or history suggestive of typical immunodeficiency disorder, a specific immunodeficiency to mycobacterium (and also presumably to candida, and borderline to tetanus) could exist. The negative results of PPD in spite of BCG infection may support this hypothesis. In our patient,

severe infections other than BCG were not observed. In disseminated BCG infections, depression of delayed type hypersensitivity may be against only tuberculin (with normal responses in vivo to candida and dinitrochlorobenzene) (16). The abundant number of bacilli in tissues with relatively good appearance and to toxic presentation may suggest specific depression of cellular defences to disseminated BCG infection. However, it is not clear whether PPD hyporesponsiveness is the cause or effect of the disseminated BCG infection.

The patient experienced a moderate regression phase after the initial left axillary lymphadenitis which first appeared at eight months of age. However, at 21 months of age generalized lymphadenitis occurred. We can not exactly explain why the biphasic course occurred. It is unlikely that the effect of the one-month INH therapy continued as long as 15 months. The temporal relationship of cessation of breast feeding and development of generalized lymphadenitis was considered coincidental.

Immunocompetent patients with BCG infection, are more likely to produce well-formed granulomas with giant cells, necrosis and scanty organisms. In contrast, patients with cellular immunodeficiency produce a poor granulomatous response with impressive proliferation of the mycobacterium (3, 6, 9, 10, 16). In our case, the nodes presented a massive infiltration of histiocytes without focal granuloma formation, giant cells or necrosis. M. bovis is generally not grown in BCG lymphadenitis. It has been isolated in only a small portion (%3-8) of BCG lymphadenitis (4, 18). There were abundant number of BCG bacilli in the nodes of our patient. Initially, the histological picture closely resembled that of Gaucher disease. Although Gaucher cells may exhibit cytoplasmic PAS positive staining, PAS positive staining of these rods in the cells and out of the cells suggested that that appearance was presumably due to acid-fast bacili. The polysaccharide consitutents of mycobacteria are oxidized by periodate to form polyaldehydes which yield red-colored compounds with Schiffs fuchsin-sulphide. Although PAS positive staining especially reveals Mycobacterium avium-intracellulare, other mycobacteria could be stained (19-21). In acquired iimmunodeficiency (AIDS) patients with disseminated Mycobacterium avium-intracellulare infection, striated histiocytes filled with mycobacteria may resemble Gaucher cells (20).

The appearence of the macrophages also resembles the view of acid-fast bacili (Hansen bacilli) proliferating in foamy macrophages as seen in lepromatous leprosy (19, 22). The clinical findings of the patient were not compatible with Gaucher disease or lepramatous leprosy. This histologic appearence is probably related to defective eradication of acid-fast bacilli in the macrophage. It may probably result from a lack of T cell-mediated immunity against BCG (10, 17, 19, 23).

In conclusion, cytological preparations of BCG lymphadenitis may resemble Gaucher disease and lepromatous leprosy. These may demonstrate impressive numbers of BCG bacilli within the macrophage that presumably have defective function against the BCG.

References

1. Rouillon F, Wealer H. BCG vaccination and epidemiological situation; a decision malking approach to the use of BCG. Adv Tuberc Res 19: 64-126, 1993.
2. Ildırım I. Sapan N, Çavuşoğlu B. Comparison of BCG vaccination at birth and at third month of life. Arch Dis Child 67: 80-2, 1992.
3. Kumar PV, Banani SF. Fine needle aspiration findings in generalized post Calmette-guerin Bacillus lymphadenitis presenting as an abdominal mass. Acta Cytol 38: 165-8, 1994.
4. Oguz F, Sıdal M, Fırat A, Neyzi O. Treatment of Bacillus Calmette-Guerin associated lymphadenitis. Pediatr Infect Dis J 11: 887-8, 1992.
5. Casanova JL, Blanche S, Emile JF, Jouanguy E, Lamhamedi S, Altare F, Stephan JL, Bernaudin F, Bordigonu P, Truck D, Lachaux A, Albertini M, Bourillon A, Dommergues JP, Pocidalo MA, Deist FL Gaillard JL, Griscelli C, Fischer A. Idiopathic Disseminated Bacillus Calmett-Guerin Infection: A French National Retrospective Study. Pediatrics 98: 774-8, 1996.
6. Dolevkova V, Viklicky J, Sula L, Kubencova D. Fetal generalized BCG histiocytosis. Tubercle 58: 13-8, 1977.
7. Katzir Z, Okan E, Ludmirski A, Sherman Y, Haas H. Generalized lymphadenitis following BCG vaccination in an immunocompetent 12 year old boy. Eur J Paediatr 1410: 165-7, 1984.
8. Pedersen FK, Engbaek HC, Hertz H, Vergmann B. Fatal BCG infection in an immunocompetent girl. Acta Paediatr Scand 67: 519-23, 1978.

9. Romanus V, Fasth A, Tordai P, Wiholm BE. Adverse reactions in healthy and immunocompromised children under six years of age vaccinated with the Danish BCG vaccine, strain Copenhagen 1331; implications for the vaccination policy in Sweeden. Acta Paediatr 82: 1043-52, 1993.

10. Trevenen CL, Pagtakhan RD. Disseminated tuberculoid lesions in infants following BCG vaccination. Can Med Assoc J 15: 502-4, 1982.

11. Catanzaro A, Melish ME, Minkoff DI. Disseminated BCG infection. J Pediatr 99: 268-71, 1981.

12. Verronon P. Presumed disseminated BCG in a boy with chronic granulamatous disease of childhood. Acta Pediatr Scand 63: 627-9, 1974.

13. Herlin T, Thelle T, Kragballe K, Borregaard B, Thestrup-Pedersen K. Sustained depression of monocyte cytoyoxicity in a boy with disseminated nontuberculous mycobacteriosis. J Pediatr 99: 264-7, 1981.

14. Duriseti L, Galant S, Morozumi P, Green G Lehrer R, and Shimizu I. Monocyte killing defect in disseminated atypical mycobacteriosis. Clin Res 26; 184A, 1978.

15. Collins FM, Watson SR. Suppressor T-cells in BCG infected mice. Infect Immun 25: 491-5, 1979.

16. Abramowsky C, Gonzales B. Sorensen RU. Disseminated Bacillus Calmette-Guerin; infections in patients with primary immunodefiencise. Am J Clin Pathol 100: 52-6, 1993.

17. Gonzalez B, Moreno S, Burdach R, Valenzuela MT, Henriquez A, Ramos MI, Sorensen RU. Clinical presentation of Bacillus Calmette-Guerin infections in patients with immunodeficiency syndromes. Pediatr Infect Dis J 8: 201-6, 1989.

18. Parveen KN, Smikle MG, Prabhakar P, Pande D, JWohnson B, Ashley D. Outbreak of Bacillus Calmette-Guerin-associated lymphadenitis and abscesses in Jamaican children. Pediatr Infect Dis J 9: 890-3, 1990.

19. Cruickshank R, Duguid JP, Marmion BP, Swain RHA. Medical Microbiology. Volume Two. Twelfth Edition. Churchill Livingstone .Edinburg, London and New York, 1975, p45.

20. Klatt EC, Jensen DF, Meyer PR Pathology of Mycobacterium avium-intracellulare infection in acquired immunodeficiency syndrome. Hum Pathol 18: 709-14, 1987.

21. Prophet EB, Mills B, Arrington JB, Sobin LH. Laboratory Methods in Histotechnology. American Registry of Pathology. Washington, 1992, p205.

22. Lictenberg F. Infectious Disease. In: Pathologic Basis of Disease, eds. Cotran nRS, Kumar V, Robins SL.. 4th edition. WB Sounders Company. Philadelpia, 1989, pp 307-84.

23. Sidevic S. Generalized BCG tuberculosis with fatal course in two sisters. Acta Prediatr Scand 61: 178-84, 1993.