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Case Report

DISSEMINATED INFECTION WITH BACILLUS CALMETTE-GUERIN AFTER BCG VACCINATION – CASE REPORT

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Abstract. *We report a case of disseminated tuberculosis caused by a vaccine strain of tuberculosis in a five-month-old infant that presented as severe systemic infection. Unfortunately, the infant died five days after admission. After the patient's death, the diagnosis was made based on pathohistological changes and a pharyngeal aspirate culture.*

Key words: *Calmette-Guerin Bacillus, tuberculosis, infant.*

Introduction

Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis*, remains a leading public health problem worldwide [1]. In young children, tuberculosis is often disseminated due to the early, haematogenous spread of the bacterium after the primary pulmonary infection [2]. The first molecular evidence that a predisposition to tuberculosis might reflect inborn errors in immunity was provided by the occurrence of overwhelming tuberculosis in children with rare, severe primary immunodeficiencies (PIDs) [3, 4]. Disseminated disease in children with PIDs is often caused by widespread, weakly virulent mycobacteria, such as bacillus Calmette-Guerin (BCG) vaccines and environmental mycobacteria. There are some reports in the literature on patients with immunodeficiencies who developed tuberculosis [3, 4]. Complications of bacillus Calmette-Guerin (BCG) vaccination are uncommon. Fewer than one in 1000 vaccinated people develop significant local reactions, and serious disseminated disease develops in fewer than one in one million [5, 6].

Herein, we report a case of disseminated BCG tuberculosis caused by the bacillus Calmette-Guerin (BCG) vaccine in an infant who died of multiple organ failure.

Case Report

The patient was a boy that was born at term to nonconsanguineous parents of Roma origin. His birth size was normal, 50 cm and 3100 g, and he had no overt developmental defects. He was vaccinated with the BCG vaccine on the third day of life. Both parents, who had been previously vaccinated with BCG, were healthy, and he was their only child. The family's living conditions were good. The infant was healthy until 3.5 months of age, when fever and cough developed. He was hospitalised twice in a local hospital and received antibiotics due to urinary and respiratory infections. The treatment did not result in significant improvement, and the infections caused a failure to thrive.

When five months old, the infant was admitted to the intensive care unit of the Pediatric Clinic in Nis, Serbia, with fever, respiratory distress and lethargy. At the time of admission, he was severely ill and had a temperature of 39°C, a respiratory rate of 68 per minute and a heart of was 160 beats per minute. The patient was pale, underdeveloped and undernourished, and weighed 4400 g, which was below the 3rd percentile. The examination showed that he exhibited, nasal flaring, intercostal retractions, wheezing, decreased breath sounds over both lungs and granulomatous dermatitis. He was hypotonic, with modest spontaneous movements. The abdominal examination showed distension and hepatosplenomegaly.

Laboratory tests performed on admission revealed hypochromic anaemia and leukocytosis (table 1). Inflammatory parameters were high. The blood urea nitrogen, creatinine, and electrolyte levels were within normal limits. Arterial blood gas analysis showed mild respiratory alkalosis. Standard liver panel tests revealed the following results: ALT 29 IU/l (range 0–40); AST 69 U/L (range 0–40); alkaline phosphatase 346 U/L; total protein 49.4 gr/L; albumin 28 gr/L; total bilirubin 13.19 μmol/l; LDH 883 μ/l, uric acid 118 μmol/l; prothrombin time 11.5 seconds and partial prothrombin time 31.9 seconds. Immunological examination revealed

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Table 1 Laboratory findings

Variable	Reference range	At admission	4th day
Haematology			
Red blood cells ($\times 10^6/\mu L$)	4.70 – 5.80	4.08	4.06
Haemoglobin (g/dl)	11.0 – 18.0	7.8 ↓	8.7
Haematocrit (%)	51.0 – 59.0	28.8 ↓	30.7
Platelets ($\times 10^3/\mu L$)	100 – 310	200	251
White blood cells ($\times 10^3/\mu L$)	9.0 – 19.0	20.3	19.9
Neutrophils (%)	45.0 – 50.0	70.4	82.2
Monocytes (%)	3.0 – 5.0	3.0	2.4
Lymphocytes (%)	34.0 – 40.0	26.6	15.4
Biochemistry			
Total protein (g/L)	60 – 80	49.4 ↓	48.7
Albumin (g/L)	30 – 51	28 ↓	28.9
Parameters of inflammation			
C-reactive protein (mg/dl)	0 – 5	166	121
Fibrinogen (g/L)	2 – 4	6.79	/
Capillary blood gas analysis on FiO2 40%			
pH	7.35 – 7.45	7.52	7.54
PkO2 (mmHg)	60 – 80	39↓	48↓
PkCO2 (mmHg)	35 – 45	32 ↓	33↓
Virology, Bacteriology			
Elisa test for TORCH		Negative	/
Deep pharyngeal aspirate		*Escherichia coli*	/
Bacteriological culture		(ESBL+)	
Blood culture		Negative	/
Aspirate smear microscopy AFB		Negative	/
Mycobacterial culture		Positive: bacillus Calmette–Guérin	/
CSF analysis			
Haemorrhagic, Pandy +			
Biochemical analysis:			/
CSF glucose/serum glucose		1,5	
Cl (mEq/l)	96 – 120	120	
Cytological examination		Negative	/
Bacteriological culture		Negative	/
Immunological analysis			
IgA	0.058 – 0.858	<0.24	/
IgM (g/l)	0.264 – 1.46	0.20 ↓	/
IgG (g/l)	2.68 – 8.98	0.09 ↓	/
IgE (IU/ml)	< 15	<4.2	/

a decreased level of IgG 0.09 g/l and an IgM level of 0.20 g/l. Immunoglobulin A1 (IgA1) and IgE were within normal limits. The spontaneous and stimulated levels of reduction of nitroblue tetrazolium by neutrophilic polymorphonuclear leukocytes (NBT) were 6% and 68%, respectively. The results of the urine analysis was normal. The cerebrospinal fluid (CSF) obtained from the lumbar puncture was haemorrhagic. The blood culture was negative. A deep pharyngeal aspirate revealed *Escherichia coli* (ESBL+). The direct microscopic analysis of three deep pharyngeal aspirates for acid-fast bacilli was negative. Lowenstein Jensen culture of the deep pharyngeal aspirate identified bacillus Calmette-Guerin, but the results were not obtained until eight weeks after the patient's death.

A chest X-ray showed a slightly enlarged right hilar and perihilar and apical infiltrations (Figure 1). Abdominal sonography revealed mild hepatomegaly and prominent splenomegaly, with diffuse hypoechogenic focal changes (<10 mm) (Figure 2). CNS sonography revealed mild ventriculomegaly.

Initial therapy included fluids, oxygen, antibiotics (ceftazidime, vancomycin), and supplements, but the patent's symptoms did not resolve. The infant died due to multiple organ failure five days after admission.

Autopsy results showed granulomatous lesions in the spleen, liver (Figure 3) and skin. The pathohistological examination of the lungs showed changes typical of a cytomegalovirus infection.

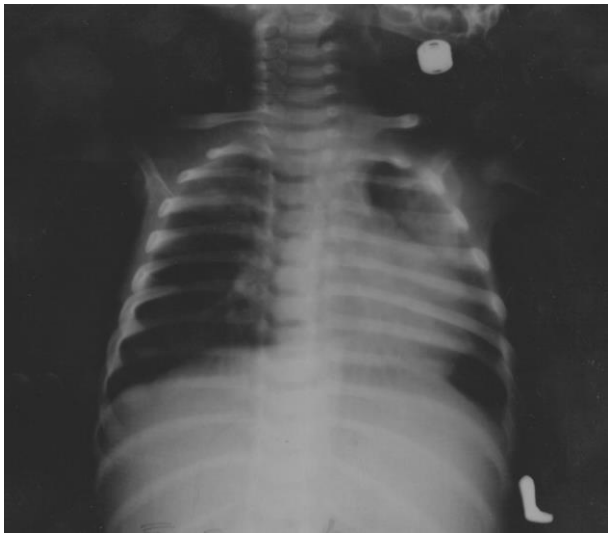

Fig. 1 Chest X-ray showed slightly enlarged right hilar lymph node and perihilar and apical infiltrations.

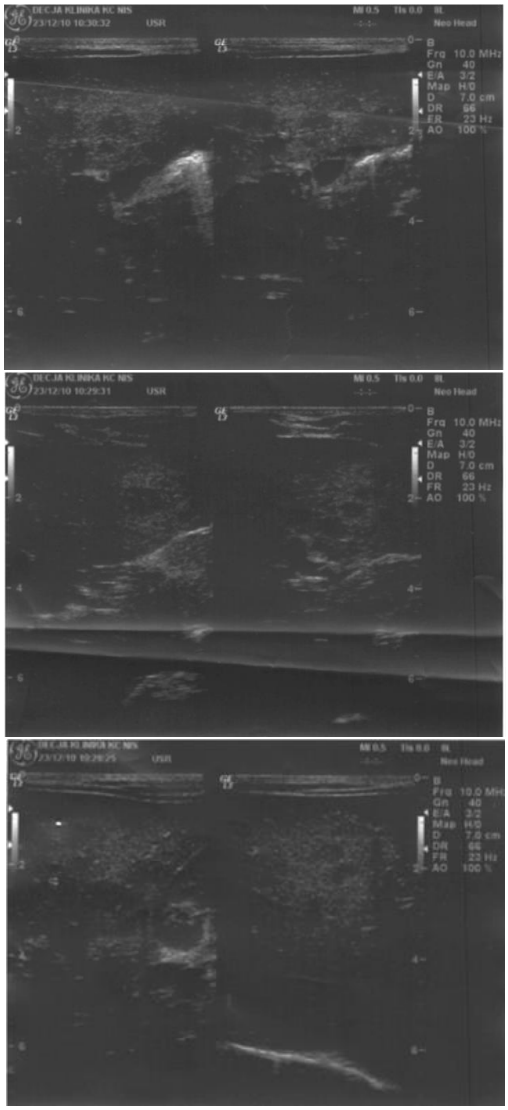

Fig 2 Mild hepatomegaly and prominent splenomegaly, with diffuse hipoechogenic focal changes (<10mm).

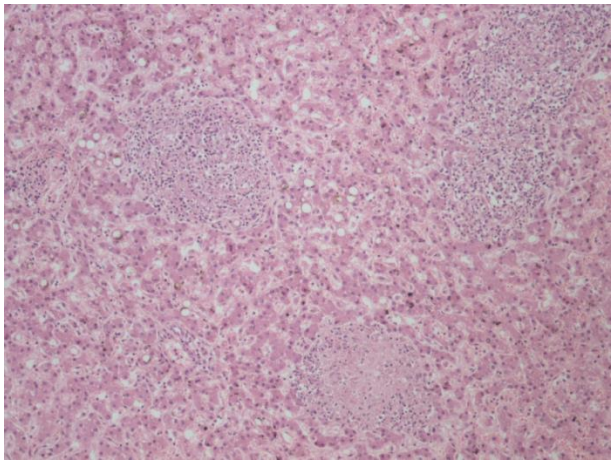

Fig. 3 There are granulomas (caseous) made of epithelioid cells in the liver parenchyma. There is caseous necrosis in the center of certain granulomas, and Langhan's giant cells (H&E 10) on the periphery.

Discussion

Tuberculosis (TB) continues to be one of the most devastating and widespread infections in the world. Young children are most likely to develop the disease after infection and are significantly more likely to develop extra-pulmonary and severely disseminated disease than adults [5].

Severe disseminated disease occurs early after the infection, within the first 2 to 6 months, and may represent an uncontrolled primary infection in children. The clinical manifestations of disseminated disease are protean, with involvement of the lungs, spleen, and bone marrow. Like adults with miliary TB, children are usually smear negative. With progressive pulmonary disease, respiratory distress, hypoxia, and pneumothorax/ pneumomediastinum may occur. Symptoms of the disease in our patients were fever, loss of appetite, respiratory distress and lethargy. The initial manifestation of disease in our patient involved the lungs, liver, spleen, and skin and included the possible early stages of meningitis.

Immunity to tuberculosis involves complex interactions between various cell populations to control and contain the infection and prevent further reactivation, but this response can also contribute to tissue damage. Cell-mediated immune mechanisms provide protection and delayed-type hypersensitivity [7]. The balance of Th1 and Th2 cytokines appears critical to controlling TB infection. Further evidence of the importance of interferon-γ can be found in children with hereditary IFN-γ receptor 1 deficiency. These children are prone to overwhelming infections with environmental mycobacteria and to the dissemination of bacilli Calmette-Guerin (BCG) after BCG vaccination. Together these data suggest that Th1 responses are protective, whereas Th2 responses are associated with chronic disease [8, 9]. In our patient, we ruled out chronic granulomatous disease using the NBT test. The serum levels of IgM and IgG were

decreased in comparison to the age-appropriate reference values. The initial treatment consisted of antibiotics, oxygenotherapy, and symptomatic therapy, that is, therapy to treat severe sepsis. Eight weeks after the patient's death, the Lowenstein Jensen culture identified bacillus Calmette-Guerin. We were not able to perform more detailed immunological tests. Cases of tuberculosis in children with malignant diseases [10, 11] and immunodeficiencies [12] have been reported in the literature, but there are few cases involving deficiencies in the receptors for interferon gamma and immunoregulatory factor 8 [8, 9, 13].

A specific immunodeficiency can be identified in only about half of the cases disseminated BCG infection [14]. In the other cases, the pathogenesis remains unclear. Such idiopathic cases have been reported in 24 countries, with a prevalence in France of at least 0.59 case per 1 million children vaccinated with BCG [15]. The high rates of consanguinity (30 per cent) and familial forms (17 per cent) and the equal sex distribution support the hypothesis of a new type of primary immune disorder with an autosomal recessive pattern of inheritance [15]. The parents of our patient are nonconsanguineous, and there were no similar diseases in other family members.

Conclusion

We have presented the case of an infant with disseminated mycobacterial disease after BCG vaccination that had a fatal outcome. Despite the use of modern diagnostics and treatments, such cases are difficult to diagnose and are even more difficult to cure. In most countries, the definitive diagnosis of macrophage function disorders (which involves analysing interleukin 12, interferon gamma, and the receptors for these cytokines and immunoregulatory factors) is difficult, which contribute to severe infections such as disseminated tuberculosis. To decrease the morbidity and mortality rates of disseminated tuberculosis caused by the BCG vaccine, further research is required to identify the basic causes of immune system disorders and to develop new therapies.

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