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Fatal BCG vaccination

By

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A female baby 7 weeks of age developed a fatal tuberculous disease following BCG vaccination. The infant had Swiss type agammaglobulinaemia, associated with oral thrush, pneumonitis, umbilical infection and chronic enteritis not responding to any treatment. Post mortem revealed an aplasia of the thymus, hypoplasia of the lymph system, miliary tuberculous foci in the lymph nodes, liver and spleen.

BCG-vaccination with fatal course is an infrequent occurrence. According to a review [23] 31 cases have been described in the literature; of these, 14 are detailed reports [1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 15, 16, 19, 20]. On the basis of the first one of the 6 cases observed in Scandinavia, Wallgren [21] assumed that a hypersensitivity of the organism was responsible for the generalized disease observed after BCG-vaccination; he excluded the possibility of an increase in virulence of the BCG strain. Subsequently in the majority of cases a congenital or acquired defect of the immune system was observed, but the mechanism of BCG-generalization is not completely clear [14].

The present paper reports on BCG-vaccination with a lethal course in an infant 3 1/2 years of age, with Swiss type agammaglobulinaemia.

Report of a Case

The female infant C. K. had been admitted at the age of 7 weeks. The family history revealed some allergic diseases in the father. The patient had been born from the mother's second pregnancy; the first pregnancy had ended with abortion. In the eighth and ninth months of gravidity the mother had been treated for heart disease. Because of postponed labour the child was delivered by Caesarean section. Her birth weight was 3300 g. BCG vaccination had been carried out on the fifth day. Simultaneously six further newborns had received the same vaccine. The infant had had no contact with any tuberculous individual. Soon after birth, the brest-fed infant had developed oral thrush refractory to all treatments. Since the age of five weeks she had daily 6 to 12 thin, mucous, greenish stools, sometimes tinged with blood.

On admission, the moderately developed baby's mouth and pharynx were thickly furred with thrush. She had a serous discharge from the umbilicus. Syndactyly of the 2nd and 3rd toes of both feet was present. She had slight bronchial rales. The site of BCG vaccination was normal and no lymph nodes were palpable.

Laboratory findings

Total serum protein, 6.0—6.2 g per 100 ml. IgA at admission, 0.19 g per 100 ml; after 4 weeks only in traces; IgA and IgM, ∅.

Blood counts: RBC, 3.800,000, WBC, 6200, platelets, 300.000. In the smears there were 33% eosinophils, 1.1% lymphocytes; plasma cells, ∅. The absolute lymphocyte count was 68. Bone marrow: normal cell count with very few lymphocytes and no plasma cells. Intact erythropoiesis and thrombopoiesis.

Chest X-rays revealed absence of thymus, and a rich pulmonary design. The Mantoux test with 100 I. U. was negative. Blood group: 0, anti A, 1 : 2; anti B, 1 : 4. Direct and indirect Coombs test, negative. The parents' blood counts, total serum protein and its fractions were normal.

In the first 3 weeks after adminission the condition was unchanged. Then the infant ran temperatures. Chest X-rays pointed to an interstitial process; a mycotic infection could not be excluded. Respiration became frequent, with dyspnoeic episodes and a choking cough at feedings. Thrush, number and quality of stools, and umbilical suppuration remained unchanged. Otitis and in the last week of the disease pustulosis and pemphigoids appeared, the left knee was swollen.

Repeated doses of gamma-globulin, transfusions of blood, intensive antibiotic and antimycotic treatment were ineffective. In the lack of an appropriate donor there was no possibility for bone marrow grafting and the planned transplantation of a fetal thymus could not be performed because the infant died in a septic state at the age of 3 1/2 months.

Post mortem. Numerous yellowish-white tubercles of pinhead size were seen in the inferior lobe of both lungs, in the lymph nodes, as well as in the spleen and the liver. Instead of a thymus, a flat structure of the size of a small bean embedded in fatty tissue was found. The mucosa of the oral cavity, the pharynx and the oesophagus were covered by a 2 mm thick layer of thrush.

In the lungs, spleen, lymph nodes, liver, the intestines, under the parietal and visceral peritoneum, in the kidneys and adrenal glands, and the bone marrow necrotic foci with indistinct contours, some surrounded by connective tissue were observed, with epitheloid cells in their vicinity. Some foci were composed only of epitheloid cells (Fig. 1). Ziehl-Neelsen's stain revealed masses of Koch bacilli (Fig. 2). In the structure found at the site of the thymus Hassall's corpuscles were not present, only the lobulation and the richness in heparinocytes pointed to the thymus (Fig. 3). The lymphoid tissue was hypoplastic.

Bacteriological examinations. In the spleen, great numbers of long, weakly staining, granular and plexiform myco bacteria were found. They corresponded to Mycobacterium avium or BCG rather than to the human and bovine mycobacterial types. Exact differentiation at Tuberculosis Research Institute in Prague revealed the organism to represent BCG, closely identical with that causing fatal disease in Czechoslovakia some time before [18]. From the lungs and pharynx, monilia was cultured.

Discussion

The case presented was one of Swiss-type agammaglobulinaemia, the combined immunodeficiency originally described by Glanzmann and Riniker in 1950 [10].

The symptoms characteristic of this genetic disease with both sex-linked and autosomal recessive heredity are an undifferentiated thymus with absence of Hassall's corpuscles, absence of lymphoid tissue and of lymphocytes in the tissues except in the bone marrow and blood, and

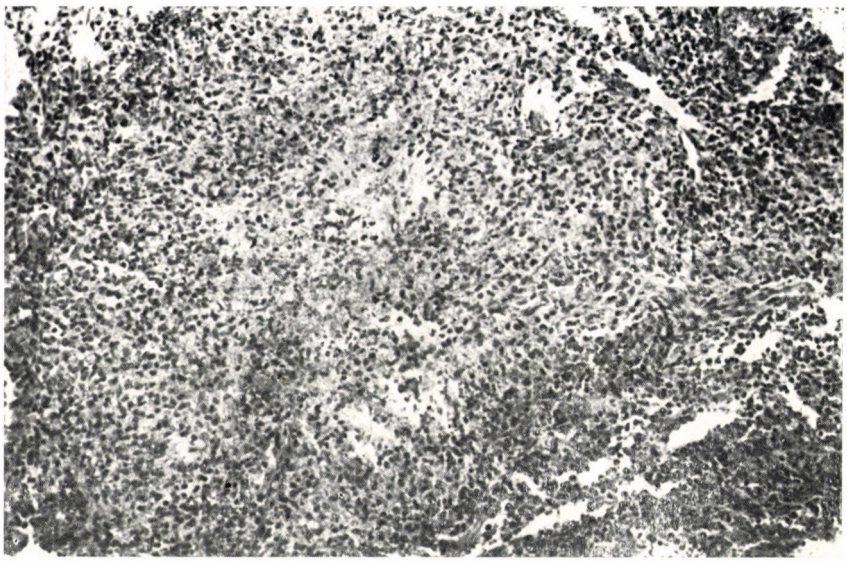

FIG. 1. Tuberculous proliferation composed mainly of epitheloid cells in the spleen (H.E.)

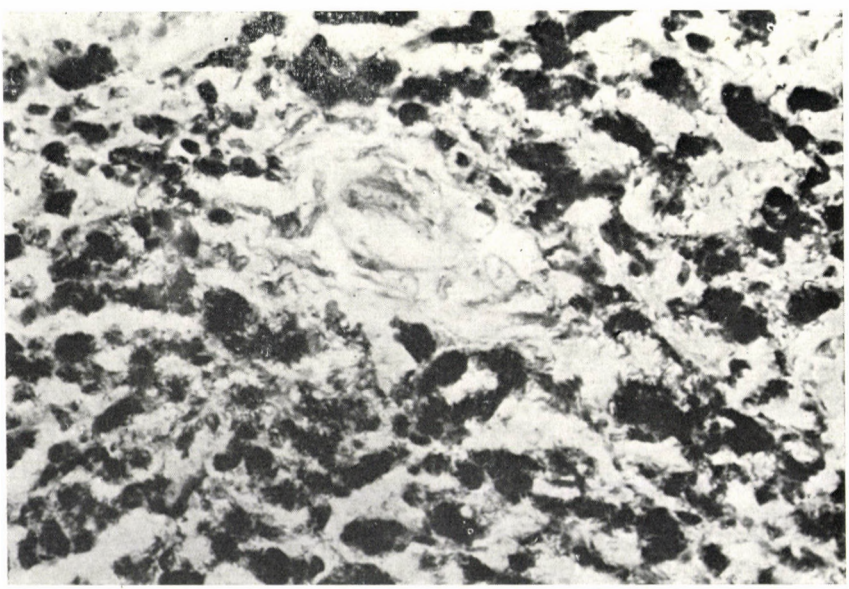

FIG. 2. Masses of tuberculosis bacilli extra- and intracellularly in a focus (Ziehl—Neelsen)

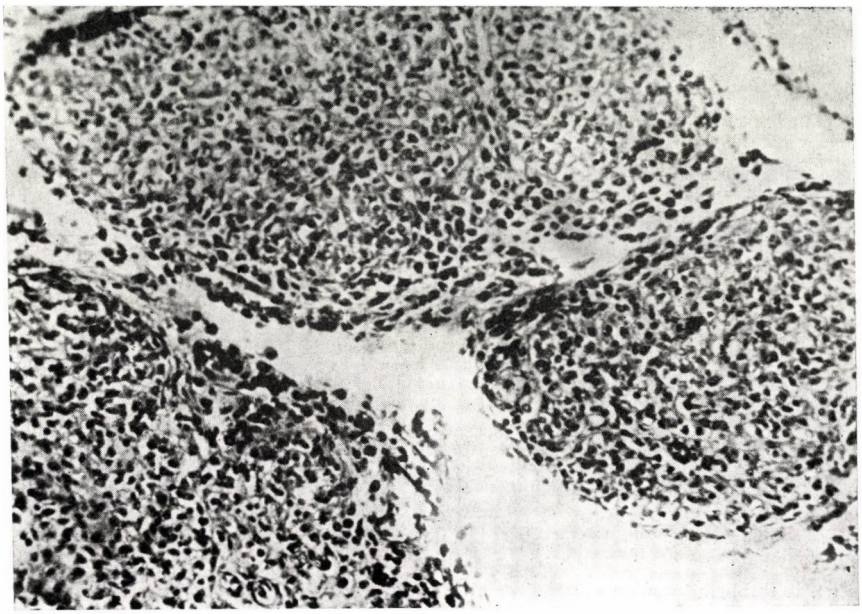

FIG. 3. Aplastic thymus of lobar structure lacking Hassall's corpuscles (H.E.)

TABLE I

Fatal BCG vaccinations

Author (s)	Age at vaccination, sex	Age at death, months	Absolute lymphocyte count.	Mantoux 100 I. U.	Serum gamma globulin	Thymus aplasia or hypoplasia
1. Falkmer et al. Sweden 1955	4 days, male	8	1620	neg.	Ø	+
2. Bouton et al. England 1963	4 days, male	9	630	neg.	Ø	?
3. Carlgren et al. Sweden 1965	5 days, male	9	1000	neg.	Ø	+
4. Veslot et al. France 1966	newborn, male	9	2000	neg.	Ø	+
5. Sičevič Jugoslavia 1972	4 days, female	47	984	neg.	normal values	+
6. Sičevič Jugoslavia 1972	no vaccination, female	34	1300	neg.	normal values	+
7. Present case Hungary 1972	5 days, female	3 1/2	68 0 124 112	neg.	Ø	+

chronic infections, especially pneumonitis and oral thrush, refractory to treatment. The disease is fatal within two years. Death is usually due to some infection, and not infrequently to generalized disease following smallpox or BCG vaccination. The only survivors have been cured by infusions of bone marrow cells from a HL-A identical donor and grafting of fetal thymus, and treatment in a germ-free environment.

In the literature, 14 cases of BCG sepsis have been reported, the majority before immune electrophoresis and other appropriate tests had become available. Of the 14 cases, 6 have been reported in detail [7, 2, 3, 20, 17]. Some of their data are shown in comparison with the present case in Table I.

A case remarkable for its epidemiological aspect has been reported by Sičevič [17]. In this child displaying a partial immune deficiency, fatal generalized BCG disease developed without previous vaccination; the infection must have been natural.

These cases have to be differentiated from BCG osteomyelitis and osteoarthritic diseases occurring in immunologically normal patients. The origin of such complications is obscure; as an explanation, a transitory immunological weakness has been assumed [8, 22].

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