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Generalized varicella in severe combined immunodeficiency with B lymphocytes

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A six-month-old male infant, whose elder brother had died of progressive vaccinia due to combined immunodeficiency, contracted varicella-zoster infection, and died of disseminated varicella ten days after onset of the disease. As with his elder brother, the blood levels of immunoglobulins were normal, and specific varicella antibodies appeared in his serum, although in low concentrations. His T-lymphocytes, although their number was subnormal, could be stimulated with phytohaemagglutinin, and production of migration inhibitory factor could also be demonstrated. The necropsy confirmed thymic dysplasia. In addition to histological changes, severe combined immunodeficiency and foci of malignant lymphoma were present. On this basis the disease was classified, according to the WHO recommendations, as severe combined immunodeficiency with B lymphocytes, complicated by malignant lymphoma.

Introduction

Varicella-zoster infection is generally a mild, benign disease mostly without complications. The majority of the fatal outcomes occurs in the so-called high-risk cases, affected by malignant disease or by primary immunodeficiency [1, 2, 9]. Chickenpox infections with especially severe course have been observed during intensive cytostatic treatment of malignant disorders, in clear relationship with the depressed number and function of the T cells [6]. The fatal outcome of varicella is attributed to the defective cell-mediated immune response even in cases of primary immunodeficiency.

In 1978 we reported the case of a boy suffering from combined immunodeficiency, who had died of progressive vaccinia [8]. The brother of the reported patient has subsequently been admitted to our department for having contracted varicella.

Report of a Case

Cs. L. a six-months-old boy with 3700 g birthweight had not been ill until the age of five months. He had been immunized with BCG and diphtheria-pertussis-tetanus triple vaccine. At the age of five months he had been treated for enteritis and pneumonia in a hospital. The course of the

diseases did not show any extraordinary features. The boy had contact with a patient having varicella but was not given zoster immunoglobulin.

The patient was six months old when he was admitted to our department, with a few varicella vesicles on his skin. Extensive mycotic dermatitis was present in the genitogluteal area, thrush was observed on his buccal mucosa. Some slightly enlarged lymph-nodes were palpable submandibularly, the liver showed an enlargement of 2 cm. In the first four days the course of varicella was normal, there was only moderate dissemination, crust formation had already appeared on two small pustules. The mucocutaneous mycosis improved markedly on local treatment. On the fourth day after admission fever and cough developed. The chest X-rays revealed a bilateral diffuse infiltration. No thymic shadow could be differentiated. Antibiotic therapy was started.

From the fourth day on the patient's condition gradually deteriorated. New varicella vesicles appeared, and on the ninth day after admission the whole body was covered by them. No regular crusts developed, on the tenth day several necrotic, haemorrhagic pustules appeared. Simultaneously the mycosis of the skin and the mucosa reappeared and spread gradually. Proteinuria and erythrocyturia appeared, the renal function tests, however, remained normal. The patient's anaemia, observed at admission (Hgb 5.15 mmol/l), remained unchanged, the platelet counts and coagulation factors were normal. Thymosine and transfer factor therapy was planned, but neither was available at that time, thus levamisole treatment was introduced on the sixth day, and zoster immunoglobulin was administered on the seventh day. The infant died on the eleventh day of his illness.

Immunological tests were performed before starting the immunotherapy. Absolute lymphocyte count, 1200. Serum immunoglobulin levels (the normal values of our laboratory are indicated in brackets): IgG: 7950 mg/l (4420 – 8900), IgM: 1320 mg/l (310 – 770), IgA: 620 mg/l (190 – 550). Surface immunoglobulin bearing cells identified by polyvalent anti-immunoglobulin: 19% (16 ± 4). E-rosette forming cells: 45% (61 ± 17). *In vitro* proliferative response of lymphocytes characterized by the PHA stimulation index: 30 (controls: 27). Leukocyte migration inhibition with PPD: 0.61 (0.80). Delayed hypersensitivity reaction to PHA: negative; to PPD: negative. The titre of serum antibodies against varicella-zoster membrane antigen was measured by immune fluorescent technique (V—Z IFAMA) on the fourth and seventh days with the same results: IgG: 1/10, IgM: 1/8.

At necropsy typical findings of generalized varicella were observed. In addition to the skin lesions several clearly demarcated round tissue defects with a few millimeters in diameter were found in the mucosa of the oral cavity and colon. The pul-

monary tissue and subpleural region contained a great number of vesicles of similar size with light-yellow content. Similar subcapsular changes were present in the liver and the spleen. The thymus weighed 1.5 g, the spleen follicles were hardly discernible.

Histology. In the thymus the number of lymphocytes is low, without corticomedullary distinction. No Hassal-bodies are present. In the lymph-nodes, no follicles and germinative centres, only groups of lymphocytes are seen but these lymphocytes are different from the normal ones. In the spleen the basic pattern is discernible, there are few lymphocytes. Lymphoid proliferation is seen, the lymphoid cells are of precursor appearance. In all organs there is increased vascularization, no necrotic areas can be seen. Liver: the histological pattern corresponds to that of malignant lymphoma. Lymphoid proliferation fills up several portal areas, similar cell clusters are found in other places, too. Several extensive foci consisting of similar cells are seen in the lungs, a smaller number of them in the kidneys. The lungs exhibit pneumonia without granulocytes. In all sections of the intestinal tract including the villi, many lymphocytes are present. In Peyer's plaques stimulated lymphoid cells can be seen. Skin: intraepithelial lytic necrosis, in the adjacent epithelial cells balloon degeneration and shrunken eosinophils. The nucleus is enlarged is most cells and in a great number of cells an eosinophilic intranuclear inclusion is present.

Discussion

The fatal outcome may be attributed to a congenital immunodeficiency. The pathological basis of primary immunodeficiency is thymic dysplasia. From the pathological findings of the thymus, spleen and lymph-nodes, considering also the observation made in the case of the patient's dead brother, an inherited immunodeficiency can be assumed. This can be classified according to the principles of World Health Organization [11] as severe combined immunodeficiency with B lymphocytes, with X-linked or autosomal recessive inheritance [3]. The fact that both patients were boys is compatible with the X-linked recessive mode of transmission. Further scrutiny of the family-tree neither excluded nor confirmed this possibility. The patient's mother had no brothers, her sister has a healthy daughter. No case suspect of immunodeficiency could be traced in either parent's family.

In this patient the course of varicella showed no extraordinary features during the first three days, no clinical signs heralded the subsequent severe events. Although the coexisting mucocutaneous mycosis suggested an eventual immunodeficiency, the rapid improvement on local treatment and the result of immunological tests seemed to speak against the presence of a severe immunodeficiency. From the fifth day the course of the disease already corresponded to severe disseminated varicella, frequently observed in immunodeficient

patients [2, 5]. The reappearance of mycosis also indicated a compromised defense-system of the patient.

At this time specific therapy was considered. Cytosine-arabinoside [4] could not be used due to its immunosuppressive effect. Treatment with transfer factor seemed to be indicated [10], but the experience with the patient's brother suggested that for the effectiveness of transfer factor a sufficient number of functioning T lymphocytes would have been necessary. This opinion was supported by observations with specific anti-varicella-zoster virus transfer factor treatment of leukaemic children [7], where specific cellular immunity could not be achieved in relapse, only during remission. Restoration of immune functions by thymic or bone marrow transplantation was not practicable because of the rapid progression of the disease, thus thymosine treatment seemed to be the only possibility for increasing the number of T lymphocytes. Unfortunately, thymosine and transfer factor were not directly available and our patient died before special treatment could have been initiated. The necropsy revealed extensive lymphoid proliferation in most organs, accompanied by signs suggesting malignancy, in addition to the severe combined immunodeficiency and disseminated varicella. Coexisting malignant lymphoma is thought to be a frequent complication of primary immunodeficiency [11]. Although the infant's survival was menaced by the malignant lymphoid proliferation itself, the immediate cause of death was a dissemination of varicella infection.

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