

GRAFT vs. HOST REACTION IN A NEWBORN

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Abstract. Graft versus host reaction has recently been reported to occur in human infants. This case report of congenital graft versus host reaction in evidence at birth illustrates the characteristic findings of this immune deficiency disease: dermatitis, recurrent infections, immunoglobulin abnormalities, diarrhea, anemia, hepatosplenomegaly and retarded growth. Clinical and laboratory criteria useful in differentiation from other disorders which present with similar skin eruptions are summarized, and possible methods of treatment are outlined.

In 1916, Murphy (11) described graft versus host (GVH) reaction as an experimental finding in chicken embryos. It was not until the 1960s that clinical cases of this immunological deficiency disease were recognized and reported (5, 12). Today, GVH reaction, which is also known as runt (16) or secondary disease (8), is a well-defined clinical entity which can occur congenitally or as a result of therapeutic manipulations (3).

This study reports an infant who was presented to our Clinic for consultation because of an unusual symptom complex which included an undiagnosed dermatitis present since birth. Various diagnoses including immunological abnormalities were considered; however, the diagnosis of GVH reaction was not established until autopsy. Because of the infrequency of this presentation the symptomatology is summarized and the etiology reviewed. In view of recent advances in immunology, it is particularly important that dermatologists recognize unusual manifestations of a disease which has become amenable to therapy in certain instances.

CASE REPORT

Clinical summary

This Caucasian female, product of an uncomplicated pregnancy, was born at term to normal parents. At birth,

the infant's skin showed a generalized erythematous, papular eruption which subsequently developed into vesicular lesions. The lesions improved with extensive topical corticoid therapy, but did not clear. During the first 2 months of life, the infant suffered from repeated episodes of vomiting, diarrhea, bronchopneumonia, and urinary tract and ear infections which responded to antibiotic therapy.

Because of recurrent infections, at 3 months of age the child was admitted and extensively studied at another hospital. Liver biopsy showed moderate fatty change with multiple non-caseating granulomas; skin biopsy revealed increased histiocytes in the dermis and an absent granular cell layer. Bone marrow findings were a myeloid to erythroid ratio of 10:1 with an increase of immature myeloid forms and histiocyte-like cells. Her immunoglobulin G (IgG) was low; immunoglobulin M (IgM) was absent, and immunoglobulin A (IgA) was within normal limits. She was anemic and therefore received to blood transfusions which led to a paradoxical deterioration of her condition.

At age 8 months, the child was transferred to the University of California Medical Center from another hospital because of increasing respiratory distress secondary to what was felt to be bronchopneumonia. At this time the child's height and weight deviated 3 standards below the mean. Apart from a slight inspiratory stridor, generalized erythroderma with areas of exfoliation and patches of small red papules, severe corrugation of the nails and scaling of the scalp and face, as well as pronounced hepatosplenomegaly were noted on physical examination. The developmental history revealed a modest degree of motor and mental retardation. Pertinent laboratory data included: chest X-ray which showed bilateral patchy parenchymal infiltrates, white blood cell count of 14 000 with 49% eosinophils, lactic dehydrogenase 616 international units (IU)/100 ml, serum glutamic pyruvic transaminase 138 IU/100 ml, serum glutamic oxaloacetic transaminase 113 IU/100 ml and platelets 676 000.

The child presented a diagnostic enigma although Letterer-Siwe disease was the diagnosis most favored. She improved on ampicillin until 8 days after admission when she became febrile, dyspneic and cyanotic. Although the histopathologic findings were not clearly diagnostic of histiocytosis-X, a therapeutic trial of vinblastine sulfate and corticosteroids with methicillin coverage was initiated

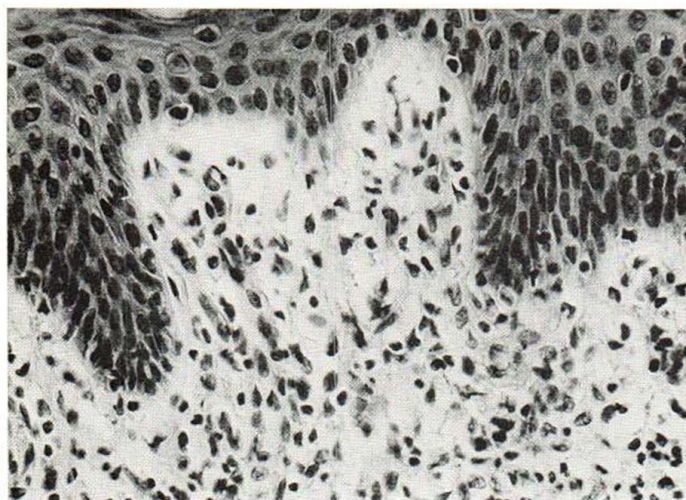


Fig. 1. Skin biopsy shows a uniform mononuclear cell infiltrate limited to the upper dermis. The epidermis contains a few dyskeratotic cells, but is otherwise unaffected. $\times 215$.

because of the child's rapid deterioration. She improved slightly on this regime; 2 days later she again became febrile, developed increasing respiratory distress and tachycardia, and expired the following day.

Autopsy findings

At autopsy, the child appeared small for her age; there was sparse hair growth on the scalp. On cross section, the lungs showed a diffuse interstitial process involving all lobes; purulent material could be expressed from the parenchyma. The only other abnormal macroscopic finding was acute congestion of the liver.

Histological examination of the lungs demonstrated areas of extensive consolidation due to bronchopneumonia, as well as pneumocystis pneumonia. The liver demonstrated only acute congestion. Gut-associated lymphoid tissue was absent in the intestine.

Microscopic appearance of the lymph nodes was uniform in the absence of lymph follicles and paracortical lymphoid tissue. Only reticulum cells, fibroblasts, and histiocytes were present, as were a few giant cells and eosinophils. The spleen also had lost its lymphoid elements and plasma cells were sparse. The thymus, which weighed 1.5 g, showed an almost complete loss of lymphoid tissue and disappearance of Hassall's corpuscles. The skin, which showed no macroscopic evidence of disease, contained a superficial dermal infiltrate of histiocytes and lymphocytes. The epidermis was unaffected.¹

DISCUSSION

This patient's course points out the cardinal symptoms and signs of GVH reaction: dermatitis, recurrent infections, abnormal immunoglobulins,

diarrhea, anemia, hepatosplenomegaly, and retarded growth. The paradoxical response following blood transfusions is characteristic; these transfusions, in fact, exacerbated her condition. This case also illustrates the difficulty in diagnosis. However, GVH reaction can be differentiated from seborrheic dermatitis and histiocytosis-X (with which it is most commonly confused) if one uses the following guidelines.

Although seborrheic dermatitis may mimic the dermatological findings of GVH reaction, it can be ruled out on the basis of systemic involvement (14). Histiocytosis-X presents clinically as discrete yellow-brown papules, which frequently become hemorrhagic in the more severe Letterer-Siwe form. Furthermore, histiocytosis-X does not result in abnormalities of hair and nail growth, whereas bony defects and hormonal abnormalities not found in GVH reaction are characteristic of the histiocytic proliferative disorders (15).

The skin histology in GVH reaction does not show the pathognomonic histiocytosis-X cells, transepidermal invasion or intra-epidermal abscess formation, but rather an infiltrate of histiocytes and lymphocytes limited to the superficial dermis and basal cell layer (9, 10). The vacuolization of basal cells in GVH reaction may be severe and can lead to total destruction of this layer (4).

Etiologically, two types of GVH reaction can be distinguished. The iatrogenic form in which immune deficiency patients receive a transplant of immune-competent cells, i.e. in the form of whole blood transfusion, and the congenital type

¹ R. A. Good and R. E. Billingham both reviewed the autopsy material and concurred in the diagnosis of GVH reaction.

most probably illustrated by this case. The latter type is thought to be due to an immunological abnormality in the fetus which allows maternal lymphocytes normally present in fetal circulation to establish themselves in the fetus and reject their host. Therefore, in cases where the affected newborn is a male, a definitive diagnosis of GVH reaction can be made on the basis of XX/XY chimerism in lymphoid cells of the peripheral blood of the child (3). The term "chimera", from the mythical monster with a lion's head, a goat's body, and a serpent's tail, denotes an animal populated by two genetically different strains of cells (6). Thus, if karyotypes of the male infant's cells reveal an XX and XY chromosomal pattern the child exhibits cell chimerism.

In the male infant only determination of histocompatibility locus-A (HL-A) antigens, inherited as co-dominant alleles, can confirm a GVH reaction. Histocompatibility antigens are present on cell membranes and determine the fate of an allogenic graft, e.g. a kidney transplant. Tissue typing techniques using cytotoxic and agglutination assays characterize these antigens (7). The child affected with GVH reaction reveals an excess of HL-A antigens. In addition to its own set of HL-A antigens of which one-half comes from the father and the other half from the mother, the child's peripheral blood cells reveal those HL-A antigens carried on maternal cells which have crossed the placental barrier. A normal infant has only one set of HL-A antigens from each parent (1).

At birth, this infant's generalized erythroderma suggested a lengthy differential diagnosis; however, her history of recurrent bacterial infections and the presence of immunoglobulin abnormalities and retarded growth strongly pointed to an immune deficiency disease. If GVH reaction had been suspected at this point, determination of HL-A antigens in the infant's peripheral circulation could have established the correct diagnosis at a time when treatment with compatible bone marrow transplant and immunosuppression might have proved successful (2, 17).

In summary, this infant's skin disorder might have been diagnosed early in life from the available data rather than at autopsy through the finding of loss of lymphoid follicles, paracortical lymphoid tissue, and Hassall's corpuscles as well as the typical mononuclear cell infiltrate in the

skin. GVH reaction instigation of modern tissue typing techniques by the alert dermatologist can result in early detection and treatment of future cases.

While this paper was in preparation we noted a case report of probable GVH reaction presenting as toxic epidermal necrolysis (13).

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