# LEINER'S DISEASE WITH OPSONIZATION DEFECT TREATED BY FREQUENT FRESH PLASMA TRANSFUSIONS

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## INTRODUCTION

In 1908 Leiner described a syndrome in young infants characterised by intractable diarrhoea, generalised seborrhoeic dermatitis, marked wasting and recurrent bacterial infections. Recent studies have demonstrated deficient opsomic activity in the plasma of patients with this syndrome (Miller *et al*, 1968; Jacobs and Miller, 1972, and Scott *et al*, 1975). Two cases have survived with therapy using fresh plasma transfusions. We report an additional case successfully treated by this procedure.

## CASE REPORT

A male infant, K.K.M., was born at term after an uneventful pregnancy to healthy, unrelated Indian parents. Two siblings age 4 years and 6 years are alive and well. However, one other sibling died at age 2 years from measles, and another died at age 3 weeks from gastroenteritis.

At age 4 weeks, he was admitted with diarrhoea and dehydration. Weight on admission was 2.0 kg.: 0.5 kg. below birth weight. Clinical examination revealed no other abnormalities. Initial laboratory findings were: Haemaglobin 16.4 gm%, platelet count 52,000/cu mm, white cell count 20,200 cu mm, neutrophils 68%, eosinophils 1%, lymphocytes 21%, monocytes 8%, atypical lymphocytes 2%, urinalysis normal, serum sodium 118 meq%, potassium 6.3 meq%, chloride 84 meq%, blood urea 37 mg%.

There was good response to intravenous fluid therapy, and oral feeding was introduced after 2 days. On the fifth day after admission, he became dehydrated despite adequate oral intake and absence of vomiting or diarrhoea. Serum chemistries showed blood urea 80 mg%, sodium 113 mg%, potassium 7.8 meq% chloride 81 mg%, capillary pH 7.17, urinary ketosteroids 3.4 $\mu$g/24 hours, and a clinical diagnosis of adrenal insufficiency was made. The infant was managed with D.O.C.A. 2 mg daily initially and later with prednisolone 1 mg and fludrocortisone 0.2 mg daily.

One week after admission, disaccharide intolerance occurred, and feeding was changed to a fructose-based formula. Staphylococcal abscesses appeared in the parietal and submandibular areas, requiring surgical drainage and systemic antibiotics. Over the next 3 weeks he developed oral thrush, further episodes of staphyloccal pyoderma, and abscesses involving the left elbow and neck.

At age 8 weeks, complete intolerance to all sugars resulting in explosive diarrhoea had developed. A skin eruption resembling seborrhoetic dermatitis appeared initially on the arms, but then spread to all flexural areas, the scalp and eventually the whole body (Figs. 1 and 2). For the next 3 weeks, all oral feeding was withheld, and total hyperalimentation administered via peripheral veins and a jugular venous catheter. During this time he developed staphylococcal septicaemia and right thigh abscess.

When at 11 weeks old he was able to tolerate fructose-base formula, intravenous hyperalimentation was discontinued. Over the next 5 weeks he developed a series of infections: pseudomonas otitis externa, klebsiella septicaemia, bronchopneumonia on two occasions, staphylococcal abscesses, and osteomyelitis of the left fourth costo-chondral junction from which the opportunistic fungus, torulopsis glabrata, was isolated.

## MATERIALS AND METHODS

The methods used for immunological testing were routine. Serum immunoglobulins were measured by radial-immunodiffusion (Mancini *et al*, 1965). Lymphocyte transformation to phytohaemaglutin (P.H.A.) was assessed by 3H-thymidine uptake. Nitroblue tetrazolium dye reduction was performed by a semi-quantitative technique (Ochs and Igo, 1973).

Yeast opsonisation studies were performed as previously described (Miller *et al*, 1968). In brief, human leukocytes were isolated by dextran sedimentation from heparinized whole blood, and incubated in plasma and baker's yeast for 30 minutes at 37°C, and stained with giemsa for counting.

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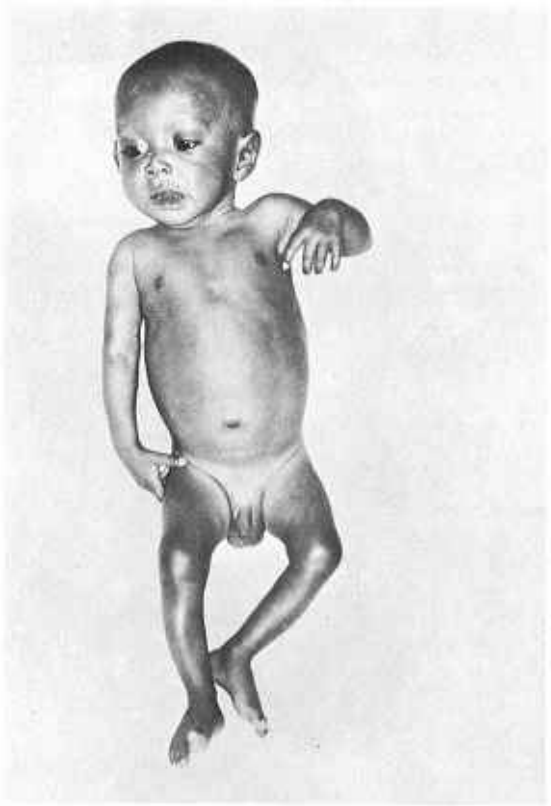

Fig. 1. Patient K.K.M. at age 16 weeks with failure to thrive, generalised dermatitis and intractable diarrhoea.

## RESULTS

The results of immunological studies on the patient at the age of 16 weeks are presented in Tables I and II. There was an increase in serum IgM for age, while IgA and IgG were normal. Lymphocyte transformation by P.H.A. assessed by 3H-thymidine incorporation, was normal. The ability of leukocytes to reduce the dye nitroblue tetrazolium was unimpaired. Serum levels of $C_3$ and $C_4$ as well as total haemolytic complement activity were normal. However, deficient opsonic activity was demonstrated in the patient's plasma (Table II). Normal plasma opsonised 90% of yeast particles whereas patients plasma opsonized only 40%. In addition, the number of yeast particles phagocytised per leukocyte was decreased compared to controls. This defect was correctible in-vitro by normal plasma.

## CLINICAL COURSE

Treatment with fresh plasma (<48 hours old) transfusions was commenced at 17 weeks of age with 10 ml/kg body weight on alternate days. Because of supply difficulties, there were several breaks in the plasma transfusion regimen, resulting in these infections: purulent arthritis of the left knee, paronychia of the left thumb, and bronchopneumonia. From the 23rd week onward, no further infections occurred, the diarrhoea and dermatitis gradually improved, and he began to gain weight rapidly (Fig. 3). Plasma therapy was discontinued at age 30 weeks. Maintenance mineralo-corticoids was discontinued at age 45 weeks when stimulation test showed normal adrenal function.

At the time of writing, the patient is a healthy toddler of age 13 months (Fig. 4). He is infection-free, has a normal skin, is tolerating a normal diet, height and weight are within the 50th percentiles, and he is functioning at the 10-11 month developmental level. Immunizations with B.C.G., poliomyelitis, D.P.T. and T.A.B. vaccines have been well tolerated.

## DISCUSSION

The clinical presentation of this patient with generalised dermatitis, intractable diarrhoea, failure to thrive and recurrent bacterial infections resembled closely three cases reported in recent years (Miller *et al*, 1968; Jacobs and Miller, 1972; Scott *et al*, 1975) in which a plasma defect in opsonization has been identified. This defect has been identified as a dysfunction of the fifth component of complement ($C_5$). A functional assay using yeast

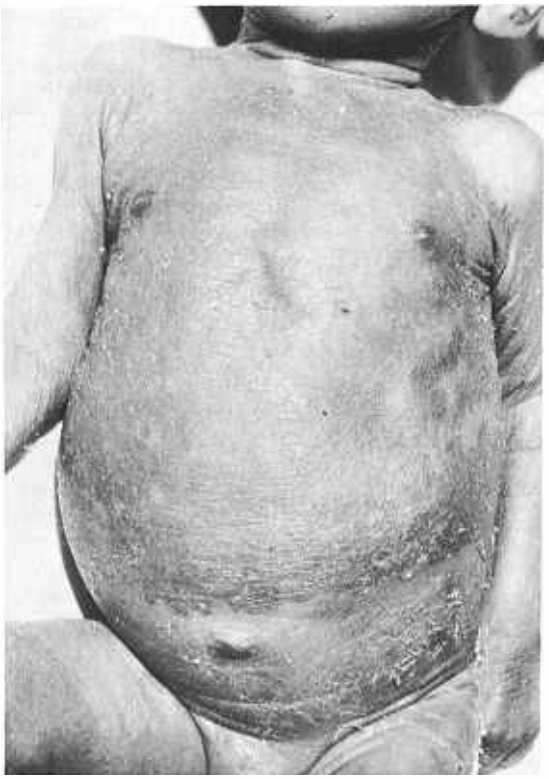

Fig. 2. Close-up of patient K.K.M. at age 16 weeks.

TABLE I

RESULTS OF IMMUNOLOGIC FUNCTION TESTS ON K.K.M.

Quantitative serum immunoglobulins

| | |
|---|---|
| IgA: | 76 mg/ml |
| IgG: | 830 mg/ml |
| IgM: | 261 mg/ml |

Antibody response to immunization with T.A.B. vaccine:

| Before | | After | |
|---|---|---|---|
| H. | O. | H. | O. |
| <1 : 8 | <1 : 8 | 1 : 64 | <1 : 8 |

In-vitrolymphocyte response to PHA: normal

Nitroblue Tetrazolium Reduction by polymorpho-nuclear leukocytes

| | |
|---|---|
| Unstimulated | 60% |
| Stimulated | 90% |

Complement studies

| | |
|---|---|
| Total serum haemolytic complement: | normal |
| Serum $C_3$: | 137 mg/100 ml |
| Serum $C_4$: | 38 mg/100 ml |

TABLE II

FUNCTIONAL ASSAY FOR $C_5$ ACTIVITY: EFFECT OF PLASMA ON PHAGOCYTOSIS OF BAKER'S YEAST

| Leukocytes | Plasma | % Phagocytosis | Yeast No. of particles per leukocyte |
|---|---|---|---|
| 1. Patient | Patient | 30 | <5 |
| 2. Control | Patient | 40 | <5 |
| 3. Patient | Control | 75 | >10 |
| 4. Control | Control | 90 | >10 |

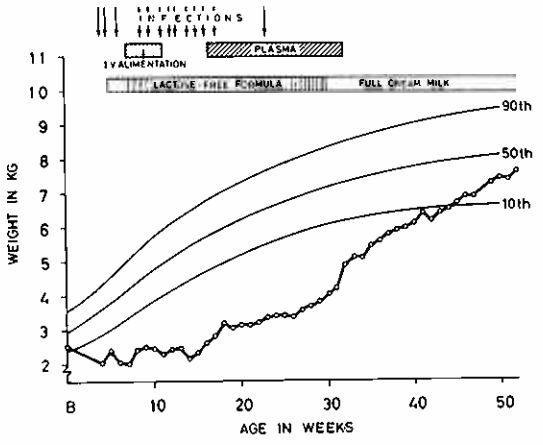


Fig. 3. Summary diagram of the Clinical Course of patient K.K.M.

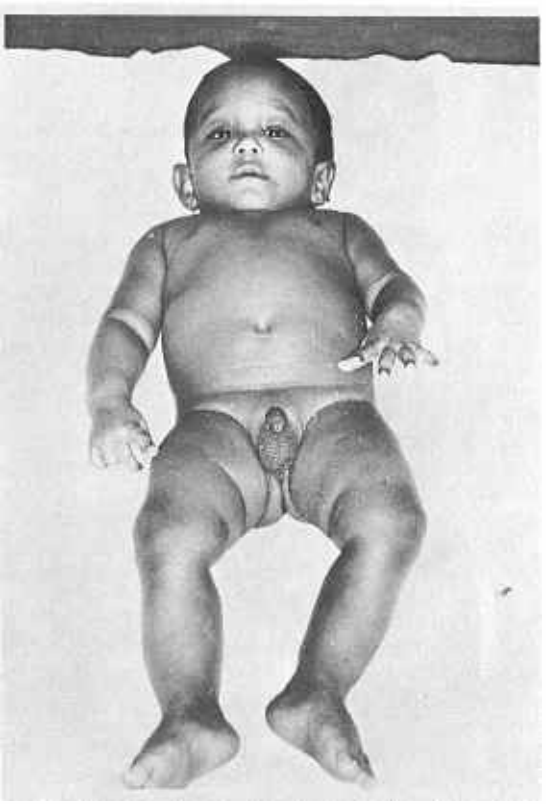

Fig. 4. Patient K.K.M. at age 13 months.

particles is necessary since immunochemical measurement of $C_5$ has been normal in affected children and their families (Miller and Nilsson, 1970). Yeast opsonization is a complex process involving the presence of $C_5$, $C_3$, serum antibody and perhaps the alternate pathway of complement activation, and it is possible that defects other than $C_5$ dysfunction could cause defective opsonization. In this regard, the case described by Scott *et al* (1975) may represent a new variant of this disease; moreover, their patient had features of the Leterer-Siewe syndrome at autopsy.

The pattern of inheritance is variable. Miller's first case, as well as the case of Scott *et al*, are thought to be autosomal dominant, whilst Miller's second case suggested an autosomal recessive transmission. The situation in our patient has not been defined.

It is mandatory that young infants with the clinical presentation of Leiner's disease be investigated by the opsonization test because of the potential benefit from plasma therapy. Our experience is similar to Miller's in that plasma transfusions can be terminated after the age of 9-12 months. The reason is unclear, but it is postulated that with increasing maturity, other components of the immune system may compensate for $C_5$ dysfunction.

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