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Treatment of Mitsuda-Negative Leprosy Patients with Transfusions of Whole Blood from Mitsuda-Positive Donors

J. C. ALMEIDA GONÇALVES AND J. CUSTÓDIO

Instituto de Assistência aos Leprosos, Lisbon, Portugal

Two lepromatous and one borderline patient improved following transfusions of whole blood from selected donors whose Mitsuda reactions were positive. Two of the patients had received no previous antileprosy therapy and remained untreated during the study. The third patient was probably drug resistant. Improvement was preceded by febrile episodes, "benign reactions", which are described.

Introduction

Present chemotherapy of leprosy is not completely satisfactory. Improvement is slow, lepromatous reactions are frequent and there is no established therapy for enhancing the immunological capacity of the patient against *Mycobacterium leprae*. However, it has been suggested by Rotberg and others that patients with lepromatous leprosy lack a genetically determined resistance factor. To test this hypothesis we postulated that patients with lepromatous leprosy, who lacked this factor, might benefit from passively transfused "resistant" cells, present in whole blood transfusions, from Mitsuda-positive blood donors. The present paper summarises preliminary results from studies designed to test this hypothesis.

Materials and Methods

The studies were undertaken on three male patients, all with active disease, two of whom were previously untreated (one with lepromatous and the other with borderline type leprosy) and the third with relapsed lepromatous type leprosy. almost certainly due to the emergence of drug resistance. A panel of blood donors who were strongly Mitsuda-positive (>5 mm) were selected and cross matched with the respective leprosy recipients. Each leprosy patient received a series of blood transfusions from a selected donor and the blood transfusions were carried out immediately after collection from the respective donors.

Case Reports

Case 1. F.A.O.P.

A 21 year old Caucasian, born in Goa; untreated lepromatous leprosy. Two months before the present study the patient suddenly deteriorated with new skin

lesions affecting the face and trunk and his vision, which had previously been normal, became blurred with excessive lacrymation. He did not notice any changes in cutaneous sensitivity or nasal obstruction. On examination his face was erythematous and infiltrated with numerous wax coloured small nodules. On the trunk there were symmetrical faint reddish copper coloured macules with indefinite edges. There was nodular infiltration of the nasal mucosa.

Bacteriological examination of skin smears and nasal mucus showed large numbers of bacilli and globi, with small numbers of bacilli in the tears. Histological examination of a biopsy from the forehead showed lepromatous leprosy, with a high BI and the majority of bacilli stained solidly. Blood examinations revealed a moderate normochromic anaemia, positive Wassermann and Kahn tests and normal serum proteins and E.S.R. Urinalysis was within normal limits. The blood group was O, Rh positive.

Treatment with transfusions of 200 ml of whole blood at 10-15 day intervals were initiated. Increased nasal obstruction was the only manifestation noticed by the patient during the first six transfusions. However, on the 9th day after the 7th transfusion the patient suddenly presented a plethora of unusual manifestations. He felt repulsed by food, vomited, and the faeces were soft and black (negative for occult blood). Nasal obstruction suddenly disappeared after the expulsion of a yellowish and gelatinous discharge from the nose. Normal vision was recovered and he felt a sensation of well-being in spite of pyrexia. On examination the redness and swelling of the face had almost completely subsided. However, he presented polyadenopathy, splenomegaly and swelling of the left testis. Because the pyrexia (38.2–40.0° C) persisted for the next four days, associated with profound asthenia and deterioration in the patient's condition, a course of prednisone (30 mg, daily) was initiated. The temperature returned to normal within two days and then the dose of prednisone was reduced and finally discontinued. In the next 20 days although the patient was emaciated and weak his original symptoms of leprosy were considerably diminished. However, there was no diminution in the number of bacilli in his nasal discharges or skin scrapes. A biopsy from the forehead, near to the first biopsy, showed a granuloma of the same type but occupying less skin area although the density of bacilli per microscope field was unchanged.

During these episodes and over the next two months a series of laboratory investigations were undertaken. All blood cultures proved negative, as did the Widal reaction, although the Wassermann and Kahn tests remained positive. The E.R.S. ranged between 23-35 mm, before returning to normal two months later. The Takata-Ara and thymol tests were positive but the Van den Berg reaction remained negative and the serum bilirubin was 0.2 mg %. The L.E. test was negative. The blood examinations revealed a normochromic anaemia with 3,750,000 erythrocytes, 75% haemoglobin and colour index 1; 18,600 leucocytes–50% neutrophils, 48% lymphocytes, 2% monocytes and 0% eosinophils and basophils. The electrophoretic serum protein pattern was as follows: total proteins 7.4 g %; albumin 45%, α-1 globulin 0.5%, α-2 globulin 10%, β 7.5% and γ globulin 37%.

Because of these unexpected manifestations no further blood transfusions were given after the 7th, and except for the short course of prednisone no specific therapy was administered. Although the patient's general condition rapidly improved, his leprosy condition seemed to slowly deteriorate after one month and was obviously worse after two months, with the reappearance of skin infiltration,

although his vision remained normal and there was no return of nasal obstruction. Therefore the series of whole blood transfusions were recommenced for a second time at a volume of 200 ml at two weekly intervals. Since after two such transfusions no recurrence of reactions had occurred the dose was increased to 400 ml for the next two transfusions. With no further reactional episodes the dose was again reduced to 200 ml. However, eight days after the 7th transfusion of the second series a "benign reaction" occurred, similar to the former but less intense. The temperature rose to only 38.4° C, there were no black stools, and there was no general deterioration in the patient's condition. Therefore this time corticosteroid therapy was not administered and he was given an 8th transfusion. This was followed immediately by swelling and pain of the left testis but no pyrexia. As previously, there was a sudden diminution in his leprosy symptoms and this time a significant fall in the BI from his nasal discharge with a high proportion of granular organisms. Specific antileprosy therapy was then initiated with Madribon and at the same time blood transfusions of whole blood were continued every two weeks for a further five months. The patient's condition has continued to improve and his Wassermann and Kahn tests have become negative without receiving any antisyphilis treatment. His Mitsuda reaction remains negative.

Case 2. F.P.M.

A 27 year old Caucasian, born in Portugal; untreated borderline leprosy. One year before this study began the patient had an indolent witlow of the left hand. At the time of our study the patient presented with lesions of the forehead, trunk and limbs. The face was infiltrated and red. There were mixed type of lesions on the trunk and limbs, some being macules with an ill-defined edge and others erythematous with very well defined edges. The nasal mucus contained a few bacilli and single globi whereas a smear from the forehead revealed a large number of bacilli and globi. The Mitsuda reaction was negative. Histology was typical of borderline (BL) leprosy (Ridley and Jopling, 1966). All other investigations were within normal limits.

Whole blood transfusions were commenced at intervals of 15 days, the first dose was 200 ml, the next four 400 ml and the following nine 200 ml.

After the 8th transfusion he had a slight reaction, without fever, characterized by repugnance against food, but without vomiting and by the appearance of enlarged axillary and inguinal lymph nodes. The symptoms lasted for seven days. Afterwards the lymph nodes diminished but the erythema and the infiltration of the face increased. He then began to improve slowly. After the 12th transfusion and six months after the first transfusion, he was much better. The infiltration of the lesions had disappeared and so had the erythema and swelling of the face. The lesions on the trunk were still present but they had a very unusual appearance. Each lesion consisted of a very clearly defined yellow oval-shaped centre surrounded by a rose coloured area, the outer edge of which was irregular and ill-defined. We were surprised at the contrast shown by the inner and outer areas of the lesion. After 14 transfusions and eight months the transfusions treatment was discontinued and the administration of 100 mg DDS a day was started. This high dose did not provoke any adverse reactions.

At the end of the transfusions treatment the smears revealed the same quantity of bacilli but half of them were granular. Histological examination showed the same structure as before but with moderate fibrosis of the superficial dermis and

many acid-fast bacilli, with a proportion granular. Routine laboratory examination remained normal. The Mitsuda reaction continued negative.

Case 3. S.N.C.

A 45 year old Caucasian born in Portugal; drug resistant lepromatous leprosy. When we first saw the patient in 1961 he had advanced lepromatous leprosy with a 25 years history, in spite of many years of irregular treatment with DDS. His skin smears were highly positive, skin histology was typical of lepromatous leprosy and his Mitsuda reaction was negative. The patient was then treated with thiambutosine and improved for one year. ENL then developed and his condition deteriorated. Treatment was changed to Madribon, he improved for two years and then deteriorated again. Throughout these three years he had continuous ENL in spite of corticosteroid therapy (5-10 mg prednisone, daily). Because we had then exhausted all the known antileprosy drugs available in this country we decided to submit him to whole blood transfusion treatment.

Whole blood transfusions of 200 ml were given at intervals of 10-30 days and Madribon therapy was continued in spite of our opinion that the drug was without effect. Some days after the 8th transfusion he noted black stools and by the 8th day he developed pyrexia (39.0° C), jaundice and hepato-splenomegaly. The patient refused hospitalization although we had diagnosed infectious hepatitis—this later proved to be incorrect. Black faeces remained for four days, pyrexia for 30 days and jaundice for four days. Transfusions were discontinued. However, in spite of the pyrexia it was possible to discontinue prednisone, *for the first time in 3 years*, without the reappearance of ENL manifestations. In the next 30-day period his general condition improved dramatically. Pyrexia was only present in the afternoons, erythema and infiltration of the face disappeared completely. The macules on the body were scarcely detectable and most of the infiltrations disappeared and the few that remained were very diminished and of a faint colour. Since then there have been no more episodes of ENL and corticosteroid therapy has never been re-instated. Blood transfusions were stopped after a period of two months, although Madribon therapy was continued. However, the patient's condition gradually deteriorated. We then started a second series of blood transfusions, but this time without Madribon. The second series consisted of 10 transfusions of 200 ml at 15-day intervals. The patient improved immediately and continued to do so throughout this period. Clofazimine therapy was then started and the patient has continued to improve.

Because this patient lived outside Lisbon only limited laboratory investigations were possible, and were confined to the period of pyrexia following the first series of transfusions. At that time blood examination showed 3.2 million erythrocytes/mm^3; haemoglobin 10.6 g %; 8300 leucocytes/mm^3 – 54% neutrophils, 32% lymphocytes, 14% monocytes and 0% eosinophils and basophils. The E.S.R was 80 mm. Urinalysis was normal and the Takata-Ara, Hanger and cadmium tests were positive. The Mitsuda reaction remained negative throughout.

Discussion

We present these three cases because the results suggest that the patients did benefit from transfusions of whole blood from Mitsuda positive donors. However, we readily admit that three cases are too few, only two were lepromatous (borderline patients can spontaneously become more tuberculoid) and complete

laboratory investigations were lacking. In spite of these limitations the results are of interest. Thus, the first case undoubtedly had untreated and progressive lepromatous leprosy which never undergoes spontaneous improvement. Yet, there was undoubtedly improvement following each series of transfusions and deterioration during the intervals when transfusions were stopped. In this case as in the other two cases improvement was associated with febrile reactions. The first and important point to exclude here is that these febrile reactions were transfusion reactions. They clearly were not because: (a) they began eight days after the transfusion, transfusion reactions begin immediately after transfusion; (b) transfusion reactions are short-lived, our reactions lasted for a month; (c) the prolonged pyrexia reactions resulting from the 7th transfusion in the first series, failed to elicit any reaction when blood from this same donor was used to initiate the first transfusion in the second series of transfusions.

The so-called "benign reactions" that resulted following a series of transfusions are not of the ENL type since they did not result in the appearance of crops of new lesions as are seen in ENL or the development of oedema of the legs and hands. On the contrary, the pyrexial episodes were associated with diminution in existing lesions, including disappearance of blurred vision and, moreover, after the first series of transfusions the patient's symptoms all returned other than blurred vision. Finally, after the second series of transfusions there was an increase in degenerate bacilli and diminution of lepromatous granuloma in the skin in a patient with lepromatous leprosy who without chemotherapy would inevitably be progressive.

Although the second patient had borderline leprosy and therefore might show spontaneous improvement, significant improvement was registered by a series of blood transfusions without any chemotherapy.

Our third case was again lepromatous, was fully active in spite of prolonged chemotherapy and therefore must have been drug resistant. Therefore, we consider that the improvement shown with the first series of transfusions in spite of continuing chemotherapy resulted from the transfusions and undoubtedly the improvement which resulted from the second series of transfusions, where no chemotherapy was given, must have been due to the effect of the transfusions. We therefore consider that the third case was as significant as the first. In addition, the third case was altered sufficiently by blood transfusions to no longer require corticosteroids, which he had previously required regularly over many years.

We consider that even this small series provides strong evidence that blood transfusions from Mitsuda-positive donors had increased the immunological capacity of all these patients and for the third case had also diminished his ENL. These beneficial effects of whole blood transfusions, particularly for the treatment of lepromatous reactions (ENL) have been repeatedly claimed by the Spanish investigators of Fontilles (Aguas, 1962, 1966; Contreras *et al.*, 1953). We claim that our very preliminary data may well be the first evidence to show that whole blood transfusions from Mitsuda-positive donors are "therapeutically" beneficial in the absence of chemotherapy.

Conclusions

(1) That the immunological capacity of a lepromatous patient can be increased by transfusions of whole blood from Mitsuda-positive donors.

(2) That this increased resistance may be due to the transfusion of immunologically competent lymphocytes.

(3) The presence of these immunologically competent lymphocytes, while sufficient to benefit the patient's bacterial infection, fail to establish a permanent Mitsuda-positive status.

(4) These preliminary and favourable results provide a possible new "imunological" basis for the treatment of patients with lepromatous leprosy.

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