Lepromatous Leprosy Presenting with Polyarthrititis, Myositis, and Immune-complex Glomerulonephritis

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Summary

A Pakistani man aged 19 years was admitted to a rheumatological unit in the United Kingdom with acute widespread polyarthrititis accompanied by night sweats and fever. Preliminary examination suggested Reiter's disease, but further investigation showed acute glomerulonephritis with uraemia. The possibility of periarteritis nodosa, and the prominence of muscle tenderness in the legs, led to biopsies of striated muscle and skin, in both of which were changes typical of lepromatous leprosy, with many *Mycobacterium leprae* on Ziehl-Neelsen staining. Serum showed IgG-IgM cryoglobulinaemia without antiglobulin activity, and in the recovery phase renal biopsy showed a resolving proliferative glomerulonephritis with linear IgG and IgM immunofluorescence and granular deposits of C3. Clinical signs subsided rapidly under steroid treatment and subsequent progress on anti-leprosy drugs was uneventful. The term erythema nodosum leprosum is inadequate and misleading as a title for a common and important immune-complex reaction of lepromatous leprosy, in which numerous body systems may be involved.

Introduction

We report here the spontaneous occurrence of type 2 (Arthus, immune-complex) reaction in lepromatous leprosy, with clinical manifestations which, though transient, were nevertheless profound.

Case Report

A 19-year-old Pakistani with a completely negative medical history during four years' residence in the United Kingdom, was admitted to the rheumatological unit at Stoke Mandeville Hospital for investigation of an acute polyarthrititis involving fingers, hands, elbows, knees, and ankles. In the four weeks before admission he had suffered concurrently from pleuritic-type chest pain, cough, mild conjunctivitis, night sweats, fever, and loss of weight. Once he had attended a dermatological clinic with a few septic spots on the hands and feet from which *Staphylococcus aureus* was cultivated and which responded completely to sodium fusidate (Fucidin ointment). Joint swelling towards the time of admission was painful, tender, and continuous. He denied sexual contact or urethral discharge and there was no history of bowel upset. Shortly before admission he had noted two minor episodes of epistaxis.

Examination showed a thin febrile man (maximum temperature 40°C) with injected conjunctivae, slight periorbital oedema, and a butterfly-distribution erythema over the face. The small joints of the hands were tender, as were the muscles generally, especially in the lower limbs, and there was spindling of the fingers with diffuse swelling of the hands, so that grip was considerably diminished. The soles of the feet and heels were tender. Splenomegaly was present (1 cm) but there was no lymphadenopathy. On the dorsum of the left hand there was an 8-mm circular macule, hypopigmented in the centre and hyperpigmented at the periphery and anaesthetic to cotton wool and pin-prick. Between the scapulae there were some vague and unremarkable erythematous macules but the skin was otherwise normal, and neither on admission nor subsequently did he show any evidence of erythema nodosum leprosum. Ophthalmological examination confirmed the presence of bilateral conjunctivitis and also showed an anterior uveitis with considerable flare and keratic precipitates. The cardiovascular system and respiratory system were normal.

A provisional diagnosis of Reiter's disease became rapidly untenable when it was discovered that he had splenomegaly and a blood urea of 40.8 mmol/l (246 mg/100 ml) with a normal serum potassium, blood urea having been 5.0 mmol/l (30 mg/100 ml) before admission. Investigations at this stage showed: haemoglobin 11.2 g/dl, erythrocyte sedimentation rate (E.S.R.) 56 mm in 1 h, blood urea 40.8 mmol/l (246 mg/100 ml), blood sugar 5.6 mmol/l (100 mg/100 ml), sodium 135 mmol/l, potassium 4.1 mmol/l, chloride 107 mmol/l, bicarbonate 11.5 mmol/l, serum creatinine 168 µmol/l (1.9 mg/100 ml), creatinine clearance 29.5 ml/min, albumin 26 g/l, and globulin 42 g/l. Electrophoresis showed increased γ-globulin. Immunoglobulins one month after admission were: IgG 39 (normal 8.8-16.8) g/l, IgM 2.05 (0.5-1.9) g/l, and IgA 1.85 (1.4-4.3) g/l. He was positive for smooth-muscle antibodies. Urinary investigations showed: daily output (average) 2240 ml, protein 640 mg/24 h, sugar up to 1%, acetone nil, red cells 82/mm³, casts nil, pus cells 9/mm³, growth nil, sodium 59 mmol/l, potassium 38 mmol/l, chloride 55 mmol/l. The following investigations were also performed but the results were normal: sheep cell agglutination test, slide latex test, gonococcal fixation test, Venereal Diseases Research Laboratory test, and blood culture. Creatinine phosphokinase antinuclear factor, and mitochondrial antibodies were also normal.

The association of an acute uraemia, without oliguria, with a multisystem disorder affecting skin, eyes, muscle, and joints suggested polyarthrititis nodosa with renal involvement. Treatment with prednisolone 60 mg and chlorambucil 4 mg was started together with 1% homatropine, betamethasone sodium phosphate (Betnesol) eye drops, and a high-calorie low-protein diet. To confirm the initial diagnosis, and because of the prominence of muscle tenderness, biopsies of striated muscle (left gastrocnemius) and skin (hypopigmented area on dorsum of left hand) were performed. The dermis showed a heavy lepromatous infiltrate with a free subepidermal zone and masses of acid-fast bacilli on Ziehl-Neelsen staining in macrophages, endothelial cells, and dermal nerve filaments. Vessels in the mid-dermis and lower dermis showed evidence of a resolving vasculitis. Polymorphs were not in evidence and oedema was not significant. Gastrocnemius was heavily involved (fig. 1), with masses of foamy macrophages and bacilli between, and often invading and replacing, muscle fibres (fig. 2).

At this point the patient was started on clofazimine (Lamprene) 100 mg three times daily. Biopsy specimens of right superficial peroneal nerve and of nasal septum taken between two and three weeks after the start of this treatment were similarly infiltrated with *Mycobacterium leprae*, and slit-skin smears from six different sites gave a bacterial index¹ (B.I.) of 4.1, and a morphological index (M.I.) the percentage of solidly-staining forms on Ziehl-Neelsen staining) of 0.5. Homogenates of biopsy specimens gave 2.0×10^8 acid-fast bacilli/g for nerve, with M.I. 2, and 7.5×10^7 acid-fast bacilli/g for muscle, with M.I. 2; a 24-hour collection of nasal mucus produced 3.0×10^5 in a blood-stained specimen, with M.I. zero. Lepromin test, using Mitsuda-type lepromin standardized to 1.6×10^8 acid-fast bacilli/ml, was negative.

In the recovery phase renal biopsy specimens showed a resolving acute proliferative glomerulonephritis, suggested by a mild diffuse

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FIG. 1—Gastrocnemius: pretreatment biopsy specimen showing infiltrate of foamy Virchow cells, lymphocytes, and plasma cells separating, and in some areas replacing, muscle fibres. *Mycobacterium leprae* are profuse in cytoplasm of infiltrating and sarcolemmal macrophages, both singly and in globi; some of the latter show central vacuolation. (Combined Masson's trichrome and Fite-Faraco. $\times 156$.)

FIG. 2—Gastrocnemius: pretreatment biopsy specimen showing numerous bacilli, some of them (S) in solid-staining (and therefore presumably viable) form lie in infiltrate between fibres. (Combined Masson's trichrome and Fite-Faraco. $\times 625$.)

FIG. 3—Kidney: biopsy specimen taken during the recovery phase showing group of non solid-staining bacilli (arrowed) associated with juxtaglomerular apparatus. (Wade-Fite. $\times 625$.)

endocapillary (predominantly mesangial) proliferation with mesangial hypertrophy and increase in tuft size involving all glomeruli. A group of bacilli were seen associated with the juxtaglomerular apparatus of one glomerulus (between the capsule and macula densa) in one section stained with Wade-Fite (fig. 3).

Renal Immunofluorescence.—There was a weak diffuse discontinuous linear fluorescence with anti-IgG and anti-IgM and a more intense diffuse scattered granular fluorescence with anti-C3 in all glomeruli. No fixation was seen with fibrinogen. Occasional tubular casts stained intensely with anti-IgA and some tubule cytoplasm granules with anti-IgE.

Cryoglobulins.—A cryoprecipitate separated at a concentration of 20 mg/l blood (about 20% not dissolving on warming to 37°C), and contained IgG and IgM, IgM forming a more intense precipitate than IgG. The cryoglobulin contained no antiglobulin activity.

The finding of ubiquitous acid-fast bacilli prompted a reassessment of peripheral nerves, and some enlargement of the right ulnar, right terminal radial at the wrist, and left lateral popliteal nerves was now evident. The whole skin surface was again checked for erythema nodosum leprosum and was found to be negative. Chlorambucil was stopped early; prednisolone was continued but gradually reduced; and rifampicin (and later dapsone) was used as the anti-leprosy drug. Within a few weeks the myalgia, arthralgia, splenomegaly, uveitis, E.S.R., and renal function rapidly and completely resolved. Bacterial indices and serial biopsies in the two years after admission showed entirely satisfactory progress.

Discussion

Though the biopsy specimen from the dorsum of the left hand might have represented a solitary (and mainly resolved) lesion of erythema nodosum leprosum, this manifestation was otherwise totally lacking in the skin of a patient whose clinical and laboratory findings pointed clearly to a spontaneous immune-complex reaction in lepromatous leprosy.

The terminology of various reactions occurring in lepromatous and non-lepromatous forms of this disease has been summarized,^{2,3} and for some years Jopling⁴ has made a plea for their division into type 1 (cell-mediated, resulting in a change of immunological status) and type 2 (humoral, with no effect on immunological status). Type 2 reactions are concerned with antigen, antibody, and complement and have features akin to the Arthus phenomenon and serum sickness.⁵ Erythema nodosum leprosum on the skin, first described by Murata,⁶ is a common but by no means invariable feature of type 2 reaction, as this patient shows. Indeed the absence of erythema nodosum leprosum was in striking contrast to the involvement of joints, kidneys, and eyes.

In one detailed study⁷ only 54.7% of 84 polar lepromatous patients developed erythema nodosum leprosum, and this "escape," often over many years of observation, is still unexplained. Equally remarkable⁸ is the fact that even when circulating immune-complexes are shown in lepromatous patients⁹ as many as a third do not develop erythema nodosum leprosum. It has often been observed that some patients have only one, or a few, mild attacks while others may be constantly afflicted; and that in some patients the same organs are repeatedly involved while in others they change with successive attacks. As far as joint involvement in type 2 reaction is concerned the published work has been well summarized,^{10,11} and in a particularly relevant report¹² concomitant myositis was present in five out of 18 cases (28%), and a notable inverse relation was recorded between the occurrence of joint and skin lesions. The heavy infiltration of striated muscle in our case was not accompanied by palpable nodules, but there were otherwise several close similarities with the patient reported by Jopling and Mehta,¹³ whose skin was also clinically unaffected.

Uraemia due to chronic glomerulonephritis is a major cause of death in lepromatous leprosy,¹⁴⁻¹⁶ and proteinuria, microscopic haematuria, cell casts, and oedema suggestive of glomerulonephritis are not unusual in reactional episodes.¹⁷ Nevertheless, leprosy has not usually been thought of as a cause of glomerulonephritis and in necropsy material¹⁸ repeated erythema nodosum

leprosum has been suspected but not proved to be the cause of nephritic changes. Recently Drutz and Gutman have published a detailed study on the specific relation of glomerulonephritis to type 2 reaction in lepromatous leprosy,¹⁹ and our findings are in accordance with their conclusions and those of others^{20 21} on the role of immune-complex deposition in glomerular basement membranes and capillary walls. The occurrence of bacilli in relation to the juxtaglomerular apparatus must be rather unusual, and though bacilli have been found in necropsy studies, and also in biopsy specimens,²² kidney parenchyma is not usually invaded in this disease. The common association of cryoglobulinaemia with lepromatous leprosy has been described,²³ and our finding of IgG and IgM in both glomeruli and the cryoglobulin suggests that they share a part in the pathogenesis of this glomerulonephritis. To our knowledge there are no published data relating the incidence of proteinuria or glomerulonephritis to that of serum cryoglobulins in leprosy, though this association has often been noted in other diseases. In conclusion the inverse relation between skin and joint manifestations in this syndrome seems to be worth further investigation, as are the effects of renal involvement on the prognosis for patients with lepromatous leprosy in reaction.

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Erythropoietic Uroporphyrria of Gunther First Presenting at 58 Years with Positive Family Studies

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Summary

Erythropoietic uroporphyrria of Gunther was seen in a 58-year-old man who presented with photosensitivity, haemolytic anaemia, and classical laboratory findings. Family studies showed five asymptomatic relatives with erythrocyte uroporphyrin concentrations in the probable latent heterozygote range.

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Introduction

After the demonstration of defects in both bone marrow and liver in erythropoietic protoporphyria¹ three major divisions of the porphyrias have been described—namely, the erythropoietic, erythrohepatic, and hepatic types.² The erythropoietic group is the rarest of the porphyrias. Only two cases of erythropoietic coproporphyrria and 70 authentic cases of congenital erythropoietic uroporphyrria (Gunther's disease) have been recorded.³ In 1962 Goldberg *et al.*⁴ wrote of the latter condition, "all cases in whom a definitive statement was made regarding age of onset presented in childhood and no patient has survived to middle age." In 1965, however, a Bantu man was reported whose first manifestations occurred when he was 55.⁵ Of all recorded cases of Gunther's disease, the man we describe here is the first in Australia, the ninth with associated thrombocytopenia, and the oldest at initial presentation.

Case Report, Methods and Results

The patient, an Australian man with British forebears, presented to a dermatological outpatient clinic in March 1965 aged 58 years. He had a three-month history of recurrent blistering of the skin of the face, scalp, and hands on exposure to the sun, plus intermittent red or dark urine. He had never been thus afflicted before. He admitted to a moderate daily intake of alcohol, but was not on any medication. There was no family history compatible with porphyria. He was married with no children. Physical examination showed a hairy man with blistering of the face, scalp, and hands. Mild facial hypertrichosis