condition proved rapidly fatal in each of their 4 patients. More recently, features similar to those of HMR have been recognized in association with two further clinical disorders. One is a benign condition secondary to viral and other infections (Chandra *et al.* 1975, Rosner 1979, Risdall *et al.* 1979), and the other is a terminal complication in patients with a pre-existing haematological malignancy (Chesney 1977, Chesney *et al.* 1978, Korman *et al.* 1979, Wick, *et al.* 1980) or carcinoma (Schumacher & Stass 1979).

The case reported here showed a very similar clinical and morphological picture to that of a highly malignant form of lymphoma. This raises the question of whether it is possible to distinguish the benign from the malignant case at presentation. Byrne & Rappaport (1973) and Warnke *et al.* (1975) stated the requirement for standard cytological criteria of malignancy in the differential diagnosis of such cases. However, there was confusion over the nature of disorders with benign cytological appearances. Risdall *et al.* (1979) reported a series of 19 patients with a potentially self-limited virus-associated haemophagocytic syndrome showing clinical similarities to the progressive histiocytic proliferations. Morphological and cytochemical criteria were proposed for distinguishing the benign and the malignant conditions.

Manoharan & Catovsky (1981) reviewed the bone marrow cytology of 19 cases with 'histiocytic medullary reticulosis' in which 15 cases had *de novo* histiocytic medullary reticulosis and 4 had the condition supervening on a pre-existing chronic lymphocytic leukaemia. The bone marrow histiocytes were graded morphologically according to their degree of maturation and their *in vivo* phagocytic activity. The authors were able to define two subgroups of patients within the *de novo* group. In one the cells appeared immature and poorly phagocytic, and these were considered to be true cases of malignant histiocytosis. In the other subgroup the cells were predominantly large and mature in appearance and exhibited marked phagocytosis. This group was considered to be reactive. Of this second group 3 cases had evidence of Epstein-Barr virus infection and recovered completely. The other 2 cases had systemic bacterial infections, and both died during the acute phase. None of the patients in the first subgroup had evidence of documented infection and only 2 cases have survived greater than one year. Assessment of the amount of bone marrow infiltration, the degree of systemic symptoms and the severity of the cytopenias was of no value in distinguishing the two groups, whereas marked hepatosplenomegaly was seen only in the malignant group.

Applying the criteria suggested by Manoharan & Catovsky (1981), it would have been possible to predict the benign nature of the histiocytic bone marrow infiltration found in this case at presentation.

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Renal transplantation in Anderson-Fabry disease[1]

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Anderson-Fabry disease (angiokeratoma corporis diffusum) is a rare, sex-linked, recessive disorder of sphingolipid metabolism. The disease is characterized by a deficiency or absence of the enzyme ceramide trihexosidase (alpha-galactosidase A), which normally catabolizes the neutral sphingolipid, ceramide trihexoside. Accumulation of the lipid consequently occurs in the plasma, and it is deposited in various body tissues including the vascular endothelium and the glomerular and tubular cells of the kidney. Progressive renal impairment usually develops in early adulthood, and uraemia is the major cause of death in the third and fourth decades. Ceramide

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trihexosidase is normally produced in most visceral tissues, including the kidney. Hence renal transplantation might not only correct the uraemia but also provide a supply of the missing enzyme and so correct the basic metabolic disorder.

A patient is described with renal failure due to Anderson-Fabry disease who received a renal transplant and in whom serum and leukocyte ceramide trihexosidase activities were measured before and at intervals up to 483 days after his transplantation. The literature relating to renal transplantation in Anderson-Fabry disease is also reviewed.

Case report

An Irish male bus driver first presented in 1974 at the age of 34 with hypertension and ankle oedema. His renal function was initially normal, although minimal proteinuria was noted. A strong family history of renal disease was elicited: one brother died at the age of 27 from renal failure, and a second brother, then aged 28, was known to have chronic renal disease. The mother of the patient is known to have suffered with high blood pressure. The patient's hypertension was treated with the alpha- and beta-blocking drug, labetalol. In view of the eye complications associated with practolol therapy he was referred for a routine eye examination. This revealed the corneal opacities which are highly indicative of Anderson-Fabry disease (Figure 1), known as corneal verticillata, together with narrow, tortuous retinal vessels. Subsequent questioning of the patient established that, since adolescence, he had suffered transient episodes of severe pain in the extremities and also an inability to sweat.

Examination of his skin revealed the characteristic angiokeratomata: dark red macules and papules varying in size from individual pinheads to areas of confluence several millimetres in diameter (Figure 2). The lesions were most profuse over the abdomen (particularly around the umbilicus), genitalia, buttocks, thighs and knees. There was a telangiectatic background to the lesions over the abdomen. Examination of the urine under polarized light showed the presence of typical lipid-laden macrophages, known as 'Maltese Cross bodies'. Skin biopsy revealed a low level of the enzyme alpha-galactosidase A in cultured skin fibroblasts (4.7 nmol/h/mg protein; normal range 78–165). These investigations conclusively proved a diagnosis of Anderson-Fabry disease.

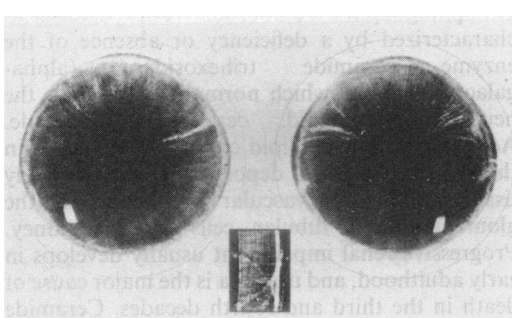

Figure 1. Corneal opacities characteristic of Anderson-Fabry disease

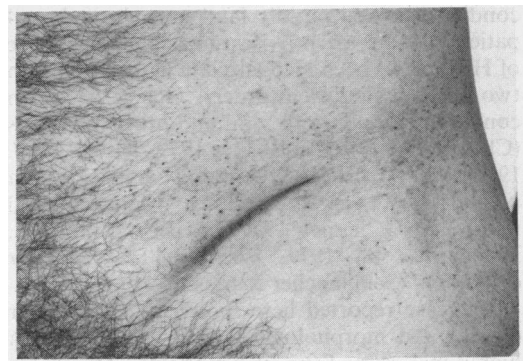

Figure 2. Angiokeratomata on the abdomen

Over the following five years there was a gradual deterioration in the patient's renal function, despite good blood pressure control. In December 1979 he suddenly became ill with gross oedema and symptoms of uraemia. His blood urea concentration was found to be 62 mmol/l, plasma creatinine concentration 1500 μmol/l and 24-hour urinary protein excretion 4 grams. Haemodialysis was therefore instigated. Three weeks later, in January 1980, he received a cadaveric renal transplant. His postoperative course was uneventful and his renal function rapidly returned to normal. In April 1980 he developed an acute nephrotic episode and a biopsy of the graft showed evidence of a mild rejection which responded to increased steroid therapy. There was no evidence of sphingolipid deposition in the renal graft on either light or electron microscopy.

The patient's ability to sweat returned to normal within six months of the transplant and he has had complete freedom from further severe limb pains. The corneal lesions appear to have decreased in number, as have the 'Maltese Cross bodies' in his urine. The skin lesions have not progressed further. However, within the first year of transplantation, the patient developed avascular necrosis of both hips which, although a well known complication of steroid therapy, has also been described in untreated patients with Anderson-Fabry disease (Wallace 1973.)

Several measurements of serum and leukocyte total alpha-galactosidase activities and of leukocyte alpha-galactosidase A activities were

Table 1. Measurements of alpha-galactosidase (αG) and alpha-galactosidase A (αGA) activities following renal transplantation

No. of days post-transplant	Serum total αG (nmol/h/ml)	Leukocytes	
		Total αG (nmol/h/mg protein)	αGA (nmol/h/mg protein)
−1 (pre-transplant)	0.50	4.20	0.10
5	0.70	2.80	0.80
16	0.60	5.30	2.70
20	0.50	3.90	0.90
30	0.80	3.80	0.10
45	1.00	2.20	0.60
50	0.90	2.00	0.10
56	1.06	5.90	1.41
112	1.02	15.30	13.60
132	0.96	7.90	6.70
151	0.96	9.60	5.80
252	0.32	2.89	1.04
378	0.53	1.41	0.60
446	3.39	2.06	1.05
483	1.15	1.17	0.54
Normal values:			
Range	8.94–39.50	37.20–152.60	30.40–141.70
Mean	24.0	82.60	74.50

performed after the patient's renal transplant (Table 1). The slope of linear regression for the serum total alpha-galactosidase activities is calculated as 0.0024 ± 0.00186 (95% confidence interval) and is significantly different from zero ($P < 0.015$). On the other hand, the slope of linear regression for the leukocyte alpha-galactosidase A activities is calculated as -0.0025 ± 0.142 (95% confidence interval) and is not significantly different from zero ($P < 0.05$). There is a wide scatter in the post-transplant activities. The discrepancy in the changes post-renal transplantation of the total alpha-galactosidase and the alpha-galactosidase A has been noted previously and it has been postulated that the isoenzyme active in cleaving ceramide trihexoside (alpha-galactosidase A) does not increase, whereas the inactive isoenzyme and hence the total alpha-galactosidase does rise (Krivit *et al.* 1972).

Discussion

Anderson-Fabry disease has many bizarre clinical manifestations and is consequently often misdiagnosed in the early stages. In childhood there may be frequent, unexplained febrile episodes associated with extreme weakness. Hypohidrosis and severe burning pains in the extremities, often triggered by changes in environmental temperature, develop in adolescence, and it is then that examination reveals the characteristic skin lesions (angiokeratomata) and, usually, an asymptomatic corneal deposition. More serious, life-threatening complications may result from involvement of the cardiovascular and central nervous systems, and of the kidneys in early adult life.

It is not unusual for the diagnosis of Anderson-Fabry disease to be made at an incidental ophthalmological examination (Bloomfield *et al.* 1978), as in this case. The corneal deposits, seen on slit-lamp examination, occur in 90% of patients and are highly indicative of the disease. They consist of creamy white, curving lines radiating from a point just below the centre of the cornea. Their presence and extent bear no correlation to the severity of the systemic involvement and they are frequently seen in the heterozygous female carriers. Conjunctival and retinal vessel tortuosity are seen in 60% of patients and lid swelling and retinal oedema in a minority. Spaeth & Frost (1965) have also described a distinctive posterior capsular cataract which occurs in about 50% of cases and which they say is pathognomonic of Anderson-Fabry disease.

Treatment of Anderson-Fabry disease was initially aimed at controlling the pain and there was no specific treatment for the disease. In the early 1970s attempts were made to correct the basic metabolic defect by replacing the missing enzyme. Transfusion of fresh plasma (Mapes *et al.* 1970) and of purified enzyme (Brady *et al.* 1973) successfully replaced the active ceramide trihexosidase but the short half-life of enzyme activity necessitated frequent transfusion, and proved a major limiting factor to this form of treatment. More recently, transfusion of fetal liver cells has been tried, with promising results (Touraine *et al.* 1979).

The clinical benefits of renal transplantation in Anderson-Fabry disease are undisputed. The correction of uraemia results in obvious improvement in the patient's general health, but perhaps more striking is the return of normal sweating and the relief from limb pains, as noted in our patient and in many others (Clarke *et al.* 1972, Krivit *et al.* 1972, Spence *et al.* 1976, Wilson 1976). There is a tendency for the limb pains to lessen and disappear spontaneously with age, but in our patient the cessation of these pains was sudden and was coincident with his renal transplantation. The exact mechanism of this improvement remains unclear. Studies of enzyme activities and ceramide trihexoside levels after transplantation have produced conflicting results. Some workers have reported reduction in plasma ceramide trihexoside levels and increase in alpha-galactosidase activity (Desnick *et al.* 1972, Krivit *et al.* 1972, Philippart *et al.* 1972), while others have been unable to reproduce these findings (Spence *et al.* 1976, Van den Bergh *et al.* 1976,

Wilson 1976). It is difficult to account for these discrepancies, but part of the reason may lie in differences in the methods of measurement and in the fact that the active A form of alpha-galactosidase may not increase, while the inactive B form does rise after transplantation (Krivit *et al.* 1972). Whatever the results of these measurements, however, striking non-renal clinical improvement is noted in nearly all cases.

Clarke *et al.* (1972) reported a drop in ceramide trihexoside levels with a parallel reduction in the levels of the precursors of ceramide trihexoside. It is known that a large proportion of the circulating ceramide trihexoside and its precursors is derived from the normal destruction of senescent red cells. Clarke *et al.* (1972) proposed that renal transplantation, by reducing the rate of red cell destruction, decreased the delivery of ceramide trihexoside to the circulation. They did not detect any rise in enzyme activities but did note considerable improvement in the non-renal manifestations of the disease.

The hypothesis that the deficient enzyme is produced within the allograft and circulated to the tissues would seem to be an oversimplification. It has been proposed that the striking clinical improvement could be accounted for by the transplanted kidney acting as a localized 'cleaving' machine for total body substrate, aided by the reduction in substrate levels as a result of increased red cell survival (Krivit *et al.* 1972). It has been suggested that enzyme replacement *per se* is unlikely to be the complete answer to the treatment of Anderson-Fabry disease since heterozygous female carriers would, on average, be expected to have 50% of alpha-galactosidase A activity and yet may suffer significant symptoms of the disease (Beutler 1979). It is noteworthy that, as in our patient, there have been no reports of sphingolipid deposition in the grafted kidney on biopsy or autopsy (Bühler *et al.* 1973, Clarke *et al.* 1972, Van den Bergh *et al.* 1976, Wilson 1976) so it would appear that the healthy graft does protect itself, preventing recurrent renal failure.

In conclusion, therefore, successful renal transplantation in patients with Anderson-Fabry disease not only corrects the uraemia but also produces marked improvement in other clinical manifestations of the disease. The mechanisms by which this happens are as yet unclear, but probably involve both reduction in the amount of sphingolipid delivered to the circulation and increased catabolism of ceramide trihexoside, either locally in the transplanted kidney or, possibly, at distant sites.

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Myocardial metastasis from carcinoma of pancreas presenting as acute myocardial infarction[1]

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A case is reported of a patient presenting with the clinical signs of acute myocardial infarction who was found to have carcinoma of the pancreas and a metastasis in the myocardium. Such presentation is unusual.

Case report

A 92-year-old man was admitted to hospital having recently developed a productive cough and

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