Renal Transplantation in Patients with Carcinoma

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Summary

Four patients in terminal renal failure who had various malignant tumours were treated by haemodialysis and cadaveric renal transplantation. One patient with a testicular seminoma and one with leiomyosarcomatous changes in polycystic kidneys were successfully grafted after removal of the tumours and both were healthy at three and two-and-a-half years afterwards without evidence of recurrence of tumour.

One patient with an invasive carcinoma of the renal pelvis was successfully transplanted and remained well for eight months but rapidly deteriorated and died of extensive metastases. Another patient with a malignant melanoma died more than one year after unsuccessful grafting.

The presence of concomitant malignant disease in patients with chronic renal failure need not necessarily exclude them from the chance of long-term treatment, including renal transplantation. Each patient should be considered individually from the point of view of the nature of the malignancy, its duration, and treatment.

Introduction

The presence of any malignant disease in patients with terminal renal failure might be considered a contraindication to renal transplantation because of the possible danger of rapid dissemination in the presence of immunosuppressive drugs. We report here on four patients with malignant tumours who underwent renal transplantation.

Immunosuppressive Therapy

All patients were treated with prednisolone and azathioprine. During rejection episodes the dose of prednisolone was increased to 200 mg/day for three days, gradually reducing to the previous level. Azathioprine was kept at the maximum level tolerated, as judged by leucocyte and thrombocyte counts, and 200 µg of actinomycin were given intravenously for three days.

Case 1

A 38-year-old farmer presented in January 1967 with sudden pain and swelling in his left testicle. On 12 January 1967 the left testicle was explored and removed. Histologically this showed the presence of a seminoma (fig. 1) and a small benign interstitial cell tumour. There was tubular atrophy of the remaining testicular tissue (Mitchinson *et al.*, 1968).

An intravenous urogram showed gross dilatation of the right ureter and pelvis, which was presumed to be secondary to obstruction at the ureterovesical junction. This was reimplemented. The

FIG. 1—Section of seminoma with sheets of large cells containing abundant cytoplasm and columns of lymphocyte-like cells. (H. and E. $\times 225$.)

left kidney and ureter were not visualized, but retrograde pyelography showed a normal ureter with a small scarred and atrophic kidney. Blood urea was 75 mg/100 ml, creatinine clearance 54 ml/min, haemoglobin 12.2 g/100 ml, and E.S.R. 39 mm/hr.

A course of postoperative radiotherapy to the para-aortic nodes was given, the kidneys and right testis being screened.

Renal function remained stable over the next year but steadily declined thereafter and he was admitted in terminal uraemia on 23 November 1970 when the level of blood urea was 332 mg/100 ml, creatinine 16.8 mg/100 ml, CO_2 8 mEq/l, Na 146 mEq/l, K 5 mEq/l, Ca 6.1 mg/100 ml, PO_4 9.4 mg/100 ml, and blood pressure 235/130 mm Hg. He was getting paroxysmal nocturnal dyspnoea, ankle oedema, tiredness, dyspepsia, and night cramps and left lower chest pain after eating food. A pericardial friction rub was audible but there were no signs of tamponade. Peritoneal dialysis was performed initially and he was later transferred to haemodialysis. There was no clinical evidence of metastatic spread from the seminoma and radiotherapeutic opinion considered it safe to subject him to renal transplantation. Bilateral nephrectomy and right ureterectomy were performed on 28 January 1971. Both kidneys showed the histological changes of endstage chronic pyelonephritis. Cadaveric renal transplantation was performed on 7 March 1971, and standard immunosuppressive therapy with prednisolone and azathioprine was used. He subsequently had normal renal function and was taking 12.5 mg prednisolone and 125 mg azathioprine a day and at the time of writing, there was no evidence of tumour recurrence.

Case 2

A 19-year-old girl presented with recurrent haematuria. Investigation showed the presence of massive polycystic kidneys. There was no family history of this condition. Angiography was performed, which showed a pattern atypical for polycystic kidneys but there were features suggestive of a neoplastic process. Infection and pain necessitated removal of the left kidney on 16 October 1970. Macroscopically the kidney appeared typically polycystic, but histological examination showed undoubted leiomyosarcomatous proliferation (fig. 2).

The remaining kidney supported life for one year with dietary protein restriction. She then had a series of epileptic attacks, and peritoneal dialysis was begun. One month later she was transferred to haemodialysis. Because of recurrent urinary infections a right nephrectomy was performed on 20 August 1971. The macroscopical

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FIG. 2—Section of the leiomyosarcomatous part of left polycystic kidney showing considerable cellular pleomorphism present in this tumour. (H. and E. $\times 225$.)

FIG. 3—Section of kidney including mass of transitional cell carcinoma on right and tumour in dilated lymphatics on left. (H. and E. $\times 90$.)

and histological appearances of the right kidney were similar to those of the left.

There was no clinical or radiological evidence of metastases. Intermittent dialysis was continued for the next two months, and on 14 October 1971 cadaveric renal transplantation was performed. Postoperative functional recovery of the allograft was delayed because of prolonged warm ischaemia time (105 minutes). A clinical diagnosis of rejection was made on the 13th postoperative day, necessitating an increase in the dose of steroids, and five days later there was a noticeable improvement in renal function.

Her subsequent course was satisfactory apart from a spontaneous left-sided pneumothorax on the 30th postoperative day. This required aspiration but it recurred two weeks later. Eventually the lung remained expanded after an intrapleural injection of colloidal kaolin. The patient remained perfectly well since then on standard doses of steroids and azathioprine. Blood urea was 42 mg/100 ml and creatinine clearance 81 ml/min at the time of writing.

Case 3

A 64-year-old office clerk had been well until November 1972 when he developed haematuria and right loin pain. An intravenous urogram showed right hydronephrosis due to pelviureteric stenosis. The left kidney seemed normal so a right nephrectomy was performed. The haematuria resolved but two months later returned and was associated with left loin pain. When repeated the urogram showed a space-occupying lesion in the left renal pelvis obstructing the lower group of calyces. The patient had lost 6 kg in weight during this five-month period and apart from lacking energy he was reasonably well. He was referred to us on 11 April 1973 for consideration for conservative surgery. The cardiovascular and respiratory systems were clinically normal. Blood pressure was normal. On abdominal examination a left renal mass was palpable. A further intravenous pyelogram and an arteriogram confirmed the presence of an avascular tumour in the region of the left renal pelvis. The chest x-ray picture was clear. An attempt at "work bench" surgical removal of this tumour and subsequent autografting (Calne, 1973) was unsuccessful in this case owing to the difficult anatomical relationships of the tumour.

Histological examination of the portion of kidney resected showed an infiltrating type of transitional carcinoma invading the peripelvic connective tissue (fig. 3) and an adjacent lymph node. The patient was therefore maintained on haemodialysis until cadaveric renal transplantation was performed on 13 July 1973. Urine output exceeded one litre by the 5th postoperative day and progress thereafter was uncomplicated. He received standard doses of steroids and azathioprine, and six months after transplantation his blood urea was 40 mg/100 ml and creatinine clearance 60 ml/min.

Two months later he developed ascites, hepatomegaly, and oedema of the lower limbs and died within a few days of admission to hospital. Necropsy showed massive hepatic metastases.

Case 4

A 56-year-old woman with polycystic disease of the kidneys and albinism went into terminal renal failure in October 1970. She was established on regular haemodialysis, and one month later bilateral nephrectomy and splenectomy were performed. The liver was noted to be polycystic. Eleven days later renal transplantation was performed and immunosuppression was started using steroids and azathioprine. Three days later the allograft had to be removed because of continued substantial haemorrhage from the operation site. Immunosuppressive drugs were withdrawn promptly and the patient was maintained on regular haemodialysis. Six months later a tender, firm, and enlarged lymphatic gland was noticed in the right femoral canal. She had had considerable shunt complications in the right leg before this and at first the enlarged gland was thought to be septic. At this time she complained of abdominal discomfort and epigastric distension, and a palpable tender hard mass was found in the epigastrium. Liver scanning with technetium 99m showed a large central filling defect in the liver. Excision biopsy of the right femoral node in June 1971 was performed, and histologically the specimen showed both purulent inflammation and malignant melanotic deposits. A small healed scar was noted at this time on the upper right thigh, which apparently was the site of removal of a mole in February 1969. Histologically this had been considered to be benign. As that operation had been performed at another hospital the details had not been available to us previously.

Regular dialysis treatment was continued for a further 10 months, during which time widespread melanotic metastases developed and the patient died in April 1972. Permission for necropsy was not granted.

Discussion

The development of malignant tumours in the recipients of organ transplants is now well recognized. "De novo" tumours may arise, malignant donor tissue may inadvertently be transplanted into the recipient, or tumour may have already been present in the recipient. The exact mechanisms underlying de novo tumour development and the part played by immunosuppressive drugs are not fully understood.

Schneck and Penn (1971) reported 52 cases of "de novo" malignant tumours in about 5,000 kidney and heart transplant patients throughout the world. Twenty-eight of these tumours were of epithelial origin and 24 were of mesenchymal origin, 11 being in the brain. The possibility of transplanting tumour tissue along with the allograft must always be considered, and living and cadaver donors should always be carefully screened. In Schneck and Penn's series it is possible that in two patients malignant tumours were present before transplantation, for metastatic spread developed very soon afterwards (Penn *et al.*, 1971).

Our patients had had malignant tumour before renal transplantation, and in such patients subsequent development of the tumour might be facilitated by immunosuppressive therapy.

It could, therefore, be argued that organ transplantation with subsequent immunosuppressive therapy has no place in the treatment of patients with cancer (*Lancet*, 1969). Total hepatectomy for primary tumours and orthotopic liver transplantation has been performed, however, with encouraging success (Starzl *et al.*, 1968; Calne, 1972) though tumour recurrences have been reported (Starzl *et al.*, 1971). In our series of liver transplants two patients who had primary malignant hepatomata were alive and well one year and six months after orthotopic transplantation with no evidence of recurrence. A third patient survived five years and had no evidence of malignant tumour when she died.

There have been very few reports of kidney transplantation in patients with previous neoplasia (Hume and Egdahl, 1955; Hume *et al.*, 1963; Hume, 1968; Woodruff *et al.*, 1969). Hume's two patients had Wilms's tumours, and both patients did well, but in one case where the time interval between removal of the tumour and transplantation was only six months tumour recurrence occurred two years later. In the other patient where the interval between tumour removal and transplantation was 12 years there was no evidence of recurrence. In the patient of Woodruff *et al.* (1969) with bilateral hypernephromata renal transplantation was performed a few days before the removal of the tumour. There was no evidence of metastases after four years (Woodruff, 1969), but the patient eventually died of recurrent growth seven years after grafting (M. F. A. Woodruff, personal communication).

Two of the patients reported here had malignant tumours of the kidneys, and transplantations were performed about two months after the removal of the tumours. In the two cases with non-renal tumours transplantation was performed two and three years after the removal of the primary tumours. In case 4 no information regarding the removal of the mole was available at the time of transplantation. The prognosis for stage I seminoma of the testis treated by orchidectomy and irradiation of para-aortic nodes approaches 90% survival (Peckham and McElwain, 1974). The decision to proceed with transplantation in case 1 was therefore entirely justified.

Sarcomatous changes in polycystic kidneys are usually considered to be noninvasive and in case 2 they seemed to be confined entirely to the kidneys, but reports of distant metastases from such tumours have been found in the literature (Lowsley and Curtis, 1945; Borski and Kimbrough, 1954; Roberts, 1973). These are rare tumours and though survival for five years after nephrectomy has been reported no information is available in regard to their prognosis.

The prognosis in patients with transitional cell carcinoma of the renal pelvis, even after removal, is poor, and when invasion of the renal substance and extrarenal structures has occurred the five-year survival rate is about 11% (Williams and Mitchell, 1973). The patient in case 3 enjoyed excellent health for eight months, but rapidly deteriorated and died within a few weeks with extensive metastases. It is difficult to assess the effect of renal transplantation and one week's immunosuppressive therapy in case 4. It is highly unlikely that she would have been considered for transplantation had the history of a previous melanotic tumour been known.

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Periurethral Enterobacterial Carriage in Pathogenesis of Recurrent Urinary Infection

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Summary

Periurethral carriage rates of enterobacteria have been studied in 20 normal women, 34 patients between episodes of bacteriuria, 34 patients with the "urethral syndrome,"

and 15 asymptomatic abacteriuric patients with a previous history of frequency and dysuria.

Over a six-week period no difference in the *Escherichia coli* carriage rate was shown between these four groups. The carriage of all enterobacteria was slightly but significantly ($P < 0.05$) lower in normal women compared with the patient groups but no difference was observed between the latter. There was no difference in the recovery rate and carriage of individual *E. coli* serotypes between the four groups.

It is concluded that the presence of enterobacteria or *E. coli* on the periurethral area is not the principal determinant factor in the pathogenesis of recurrent urinary tract infection or the urethral syndrome and that definition of carriage status is of little practical value in management.

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