

Transferral of malignancy as a complication of organ transplantation: an insuperable problem?

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SUMMARY A case of inadvertent transplantation of malignancy is presented in detail. The donor was a 36-year-old woman with an unsuspected disseminated carcinoma of lung, and the renal and tumour transplant recipient a 53-year-old man. The transplanted tumour remained clinically 'silent' and was discovered only at necropsy after the recipient's death from ischaemic heart disease. The phenomena of de novo primary and transferred (donor) malignancy in organ recipients, along with related immunological considerations, are briefly reviewed. Finally, with regard to the increasing frequency and variability of organ transplants, the routine clinical practice required to minimise the risk of these complications is re-emphasised, with additional recommendations.

The evolution of long-term treatment for the patient with chronic renal failure over the last 15 years has resulted in their present management by two major methods: chronic haemodialysis or renal transplantation of cadaveric or living related donor organs. These methods used singly or together have significantly ameliorated the prognosis for the renal patient though not without deleterious sequelae. The increased risks of serum hepatitis,¹⁻³ tuberculosis,⁴ and other infections are shared equally; however, for other reasons (*vide infra*) there is a universal preference for transplantation.

In the past, the search for donors to fulfil the overwhelming demand for organs resulted in the use of carcinomatous cadavers and the emergence of a unique complication. This, the inadvertent transplantation of malignancy, was first reported by McPhaul and McKintosh;⁵ they described in 1965 the transfer of a donor's squamous carcinoma of bronchus to a young woman recipient who later died with hepatic metastases. About the same time, Couch *et al.*⁶ published 'guidelines' concerning the use of such cadaver organs. Despite these, and an increasingly rigorous medical selection of possible donors, sporadic cases of transplanted malignancy continue. We report a case of this uncommon phenomenon to revive clinical awareness and to stimulate even greater vigilance.

The donor

HISTORY

A 36-year-old woman was admitted unconscious and areflexic with absent eye movements and fixed dilated pupils but no neck stiffness or papilloedema. Her blood pressure, pulse, and cerebrospinal fluid were all normal. A recent admission after an 'overdose' of analgesics, resulting from severe headaches, led to the diagnosis of a second 'overdose', but investigations revealed no paracetamol, salicylate, or barbiturates in the blood.

She remained unchanged, requiring ventilation for three days. Brain death⁷ was then established and her kidneys were offered for transplantation.

Both organs were removed six days after admission (Friday), offered to, and accepted through the UK Transplant Service.

NECROPSY FINDINGS

Necropsy was performed three days later (Monday). Both lungs were heavy, oedematous, tough, and rubbery, and the bronchi contained a mucopurulent exudate. There was bilateral hilar, carinal, and left cervical lymphadenopathy. A firm white tumour, 2.5 cm in diameter, was present at the apex of the right lung.

Dissection of the brain revealed a nodular mass between the cerebral peduncles. The ventricles were consequently distended by CSF. The remaining

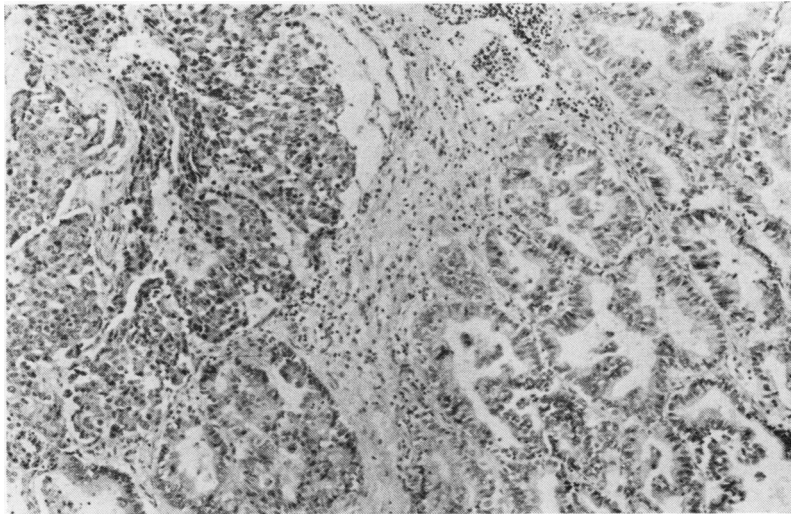


Fig. 1 A 'transitional' area of well to more poorly differentiated adenocarcinoma of the donor lung. Haematoxylin and eosin $\times 80$.

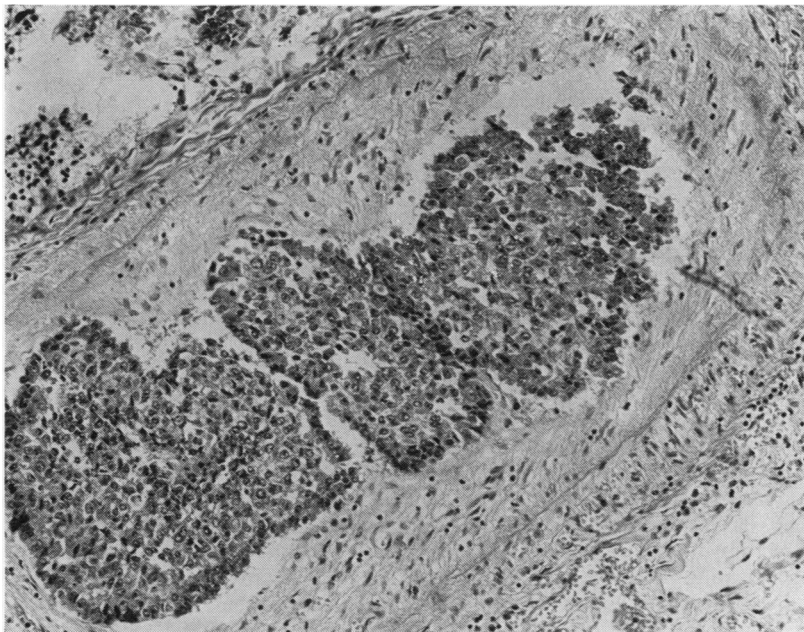


Fig. 2 A large embolus of poorly differentiated adenocarcinoma in a pulmonary artery. H and E $\times 128$.

organs showed no macroscopic evidence of metastases.

Obviously her kidneys were not examined, but no abnormalities were noted by any of the surgical

personnel involved in removing or transplanting them.

Death was attributed to hydrocephaly after aqueduct obstruction by a metastasis from a bronchial

carcinoma. At this point the UK Transplant Service was informed of the possibility of metastatic renal involvement.

Histology

Microscopy confirmed a primary adenocarcinoma of lung showing transition from a well to a poorly differentiated type (Fig. 1). There was vascular invasion, and one section revealed a large embolus of neoplastic cells in a major pulmonary vessel (Fig. 2). The cerebral nodule was confirmed as a metastatic deposit. Sections from the enlarged lymph nodes and remaining organs revealed no further metastases.

The recipient

HISTORY

A male Ukrainian immigrant aged 43 presented to his doctor in 1967, complaining of severe headaches, and was found to be hypertensive (BP 190/125 mm Hg). He remained relatively well on antihypertensive therapy for six years before developing polyuria, polydipsia, and a urinary tract infection. At this time (1973) his BP was 170/140 mm Hg, blood urea 21 mmol/l, creatinine clearance 62 ml plasma/minute and he had left ventricular hypertrophy. He was referred to the Sheffield Renal Unit where his progressive renal failure was subsequently managed, culminating with home haemodialysis in 1976. In 1977 he was referred to one of us (MF) for possible transplantation, and his name was put on the cadaver renal transplant waiting list.

In May 1978, after two-and-a-half years on haemodialysis, he underwent transplantation with one of the previously described donor's kidneys. The organ externally was not noted to be abnormal. (Her other kidney, equally unremarkable, was flown to Athens, where it was successfully transplanted but rejected by the recipient 15 days later. No further information is known to us regarding this Greek recipient.) The transplantation was technically difficult due to the recipient's severe arterial atherosclerotic disease, anastomosis of the renal artery to the external iliac artery following preliminary localised endarterectomy (MF). The right internal iliac artery contained multiple, hard, atheromatous plaques and was probably totally occluded. The right external artery was therefore used although it also was severely diseased.

During the post-transplantation period two mild rejection episodes were treated by increased doses of prednisolone. Further progress was complicated by two myocardial infarctions on the 15th and 36th postoperative days. He 'arrested' on the second occasion but was resuscitated and was eventually discharged home on the 49th day.

In view of these cardiac complications and the known extent of his arterial disease it was decided, in spite of the carcinomatous nature of the donor, to leave the transplant in situ as the risk of a second anaesthetic and operation was probably greater. He had satisfactory renal function and an acceptable standard of life for a further six months, though his cardiac condition necessitated antiarrhythmic and diuretic therapy.

In October 1978 he complained of early morning haemoptysis for two weeks and of a slight right groin ache. No abnormality of the groin or pelvis was found on examination, and this symptom rapidly disappeared. In November 1978 he was admitted with deteriorating renal function, blood urea 44 mmol/l, diagnosed as a further rejection episode. This was improved by increased prednisolone, the urea falling to 17 mmol/l. He continued to have haemoptyses, shown by lung scan to be caused by embolisation of the left lower lobe, and developed intractable heart failure and, terminally, pneumonia. In spite of treatment he deteriorated and died seven months and one week after transplantation. This was considered to be a cardiorespiratory death with no symptoms or signs referable to local or systemic malignancy.

NECROPSY

Necropsy revealed bilateral pleural effusions with heavy, congested, focally consolidated oedematous lungs. The left lung contained a friable embolus in a lower lobe pulmonary artery, confirming the lung scan report. The major bronchi contained foul smelling bloodstained mucopus, which grew coliform organisms on culture. There was cardiomegaly (weight 550 g), widespread ventricular scarring, severe atheroma of the left coronary artery, and total occlusion of the right coronary artery by fresh thrombus. Most of the aorta and its pelvic branches were replaced by complicated atheromatous plaques; the right internal iliac artery was indeed totally occluded. The liver exhibited the 'nutmeg' appearance of heart failure, and the patient's own kidneys were sclerotic (75 g each).

All the transplanted kidney's anastomoses were intact and patent, and externally it was unremarkable. Bisection of the kidney, however, revealed a vaguely demarcated, pale, focally necrotic tumour (Fig. 3). There was no macroscopic evidence of local spread or metastasis to the other organs.

These findings were consistent with the cardiorespiratory death proposed on clinical grounds. We believe that the transplanted tumour did not alter the prognosis or significantly contribute to the acute terminal events in this case.

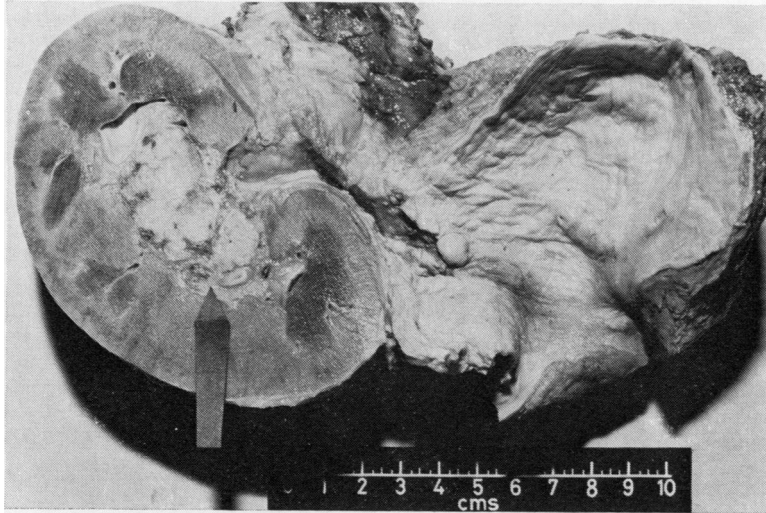


Fig. 3 *Necropsy specimen showing the donor kidney and tumour (arrowed) with the recipient's bladder adjacent.*

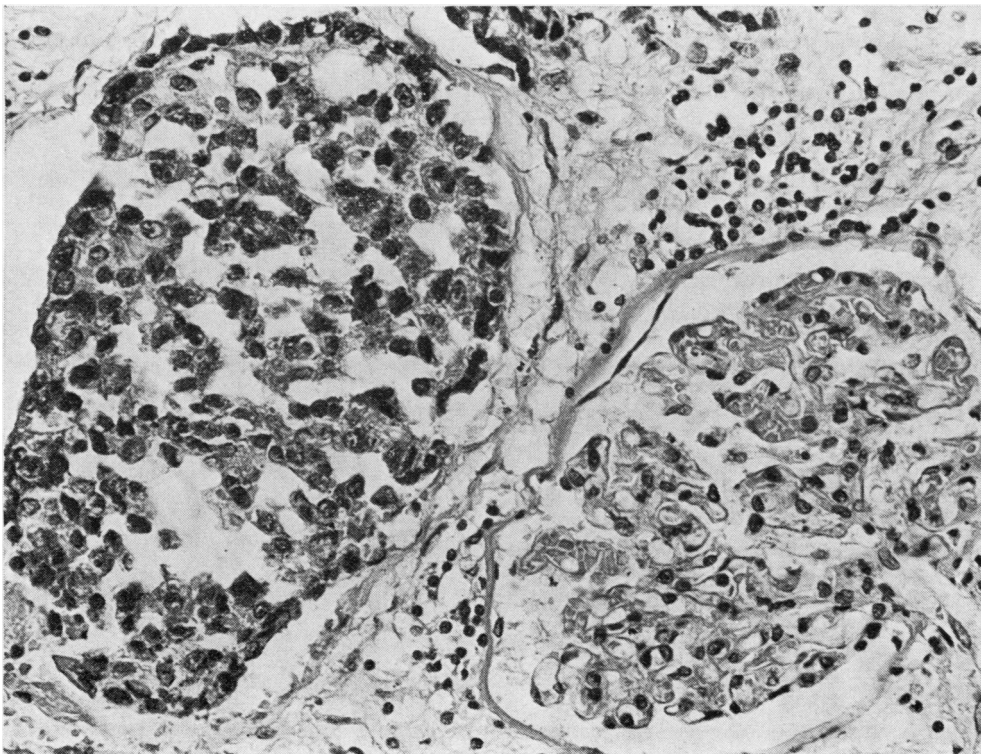


Fig. 4 *Poorly differentiated tumour adjacent to a glomerulus. H and E \times 320.*

Histology

The transplant contained an invasive, poorly differentiated adenocarcinoma (Fig. 4) with the same cytological characteristics (allowing for autolysis and fixation), growth pattern, and paucity of differentiation as the poorly differentiated areas of the donor's tumour which, we feel, establishes this as a case of transplanted malignancy.

Discussion

There are many reasons for the desirability of transplantation as opposed to haemodialysis in the treatment of chronic renal failure (see Editorial⁸ for the current status). Sufficient organ donors would make it feasible to manage all cases of chronic renal failure this way, avoiding the problems of patient 'selection' engendered by the limited haemodialysis places currently available. Though certain conditions no longer automatically exclude patients from haemodialysis (eg, see Editorial⁹), the limited resources available result in the deaths of approximately 1000 patients annually, certain regions, children, and the elderly being disproportionately represented.¹⁰

The benefits of transplantation have consequently increased the demand for organ donors. To meet this demand the public is currently exhorted to carry donor cards.^{11 12} However, at the inception of renal transplantation even patients with terminal malignancy were utilised to expand the number of kidneys available (see Martin *et al.*¹³), resulting in reports of recipients developing malignancies transferred in the donor organs.^{5 13 14}

Primary malignancies of many organs have been accidentally transplanted (for an earlier review, see Wilson¹⁵), including the kidney itself. Fox¹⁶ has even described the discovery of a primary renal tumour during laparotomy of a living related donor.

The growth and dissemination of transplanted malignancy is comprehensibly explained by the 'fertile field' provided by the recipient and is inextricably linked with the necessity for immunosuppression and close donor tissue type matching. These measures, designed to enhance graft survival, are equally beneficial to the 'foreign' tumour.

The recipient's inability to reject foreign tissue is accompanied by an increased incidence of de novo primary malignancies, a phenomenon described in both renal and cardiac transplantation.¹⁷ The types of such primary lesions are described in standard medical texts (see, for example, Meadows¹⁸ and Williams¹⁹). The incidence of de novo neoplasms in immunodepressed patients *per se*, irrespective of transplantation (see Kinlen *et al.*²⁰), suggests that their appearance in transplant recipients is directly related to the iatrogenic immunosuppression. The

significant excess of non-Hodgkin's lymphomata present in the latter group²⁰ further suggests the presence of other subtle, unknown, immunological mechanisms.

That a 'normal' immune system is deleterious to transplanted malignancy has been shown in the cases of Martin *et al.*,¹³ Wilson *et al.*,¹⁴ and Zukoski *et al.*²¹ They demonstrated, by stopping all their patients' immunosuppressants, clinical, radiological, and histological regression of the transplanted tumours. Transplanted malignancy can therefore be cured; however, its presence must first be suspected. Fortunately, the majority of reported cases have presented alerting symptoms, but some, like ours clinically asymptomatic, have been discovered only at necropsy.

Considering this case, it is arguable that, immediately upon notification of a carcinomatous donor, the transplant should have been removed, but the recipient's extremely poor cardiovascular history, especially after transplantation, seems to indicate that the decision against further surgery was in his best interests at that time. He lived for another six months with an acceptable standard of life when the alternative was, almost certainly, a cardiac death during the transplant's excision. The presence of transplanted tumour remained unsuspected and apparently clinically 'silent'.

In retrospect the recipient's complaint of a slight groin ache may have been referable to the tumour; however, it was of less than 72 hours' duration and was unaccompanied by other symptoms or signs, for example, haematuria, urinary tract infection or a palpable mass. The preterminally high serum urea (44 mmol/l) may equally have been attributable to the tumour, though it would then be difficult to explain its resolution (to 17 mmol/l) on increasing the immunosuppressive therapy, a situation, in theory, resulting in accelerated tumour growth and consequent elevation of urea. More probably, the preterminal uraemia was of multifactorial origin, metabolic imbalance, cardiac failure, and chronic rejection also contributing. Even had these two equivocal features been investigated and ascribed to a transplanted tumour, probably little could have been done to avert the eventual outcome for this particular patient.

Until more sophisticated drugs and techniques are available specifically to protect transplanted organs, primary de novo malignancy will continue as a complication for the recipient. Comparatively, the accidental transference of malignancy, though it may not be entirely abolished, may possibly be reduced in several ways.

First, the use of donors known to have had a malignancy at any time, even 'cured' long-term

survivors, is to be strongly deprecated. Necropsies on carcinomatous patients have shown metastatic renal involvement in up to 8% of cases.²² Patients with 'local' neoplasms or central nervous system tumours (themselves thought to spread only 'locally') should similarly be exempt. These latter two categories were not considered in the publication of Couch *et al.*,⁶ and Martin *et al.*,¹³ in their description of the transference of a bronchial adenocarcinoma, advise only against the use of donors with disseminated neoplasia. It is pertinent to note that central nervous system lesions may occasionally metastasise systemically.²³

Secondly, as stated previously by Barnes and Fox,²⁴ the donor must have a full laparotomy during removal of the organ. If the donor is a cadaver a necropsy should automatically follow. A similar procedure, that is, intraoperative examination and then necropsy must pertain irrespective of the organ(s) being removed: kidneys, liver, lung, heart, or skin. The necropsy should include histological examination of any suspicious abnormality with, we would suggest, immediate 'frozen-section' examination of the more disturbing lesions. These procedures are suggested to detect as many unsuspected, undiagnosed donor malignancies as possible. Occasionally, as in Fox's 'case',¹⁸ the donor organ may contain a macroscopic lesion. In such cases, frozen-section diagnosis is imperative, followed by immediate cessation of the transplantation in the event of an adverse report. If the donor is alive, management of the tumour would then become of primary importance.

It is probable that however meticulous the laparotomy/thoracotomy before transplantation, an impalpable, intraparenchymal primary tumour may occasionally be missed. Elucidation of a carcinomatous donor can then be achieved only at necropsy. We, as previously (eg, Barnes and Fox²⁴), recommend that all cadaver donors should undergo a compulsory necropsy and we further suggest that it is performed within 12 hours of the initial organ excision, irrespective of the clinical history or time or nature of death (even accidental). This may necessitate a necropsy during the night. In these circumstances, close cooperation between all the parties concerned, administrators, morticians, and medical staff, will be necessary. The shortened delay, however, would, we believe, aid the rapid notification of 'high-risk' organs, accelerating their subsequent removal, if indeed already transplanted, with fewer psychological and medical complications for the recipient. It may also be pertinent to suggest follow-up of living donors in the hope that any occult neoplasm present at the time of transplantation might reveal itself. Such tumours presenting after two years are unlikely to

have been of significance at the time of organ excision.

Lastly, we hope that the awareness of transferred malignancy among the non-specialist press and patients themselves (see Neustatter²⁵) will stimulate clinicians to be more discerning in their selection of donors, and appreciative of minor complaints from transplant recipients referable to neoplasia.

In summary, it seems that primary malignancies of transplant recipients are an unfortunate complication of their requisite therapy. Comparatively, the transferral of donor malignancy appears a relatively facile problem to overcome. We can foresee, however, that all procedures in which large tissue masses are transplanted from one person to another will inevitably result in the occasional inadvertent transfer of a microscopic nidus of malignant cells, no matter how rigorous the donor selection.

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