Segmental infarction with graft dysfunction: an emerging syndrome in renal transplantation?

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Abstract

Background. Segmental allograft infarction is a poorly characterized complication following renal transplantation. The present study was undertaken with the goal of defining the incidence, clinical characteristics, pathogenesis, and prognosis of this entity.

Methods. A retrospective study was performed, reviewing the renal scans performed on all renal transplant recipients at our institution, from January 1997 to January 2000. Segmental infarction was diagnosed on the basis of a significant elevation in lactate dehydrogenase (>500 U/l) together with a photopenic perfusion defect. In these patients, graft characteristics, operative details, clinical course, and long-term outcomes were evaluated.

Results. Segmental infarction was identified in 13 of 277 consecutive renal transplant recipients (4.7%). In nine recipients the onset of infarction occurred within 24 h after transplantation. All received marginal grafts, and in five recipients the transplant operation was complicated by major blood loss. Eight of these recipients exhibited primary non-function, or developed dialysis-dependent renal failure after the onset of infarction. In four patients, the onset of infarction occurred after 24 h (35 h to 10 days). One recipient demonstrated primary non-function, and renal function deteriorated after the onset of infarction in the remaining three. Overall, long-term graft function was impaired. Two allografts never functioned, and six recipients had nadir creatinine clearances below 60 ml/min.

Conclusions. The pathogenesis of segmental infarction appears to be multi-factorial, reflecting the combination of an initiating anatomic lesion and potentiating thrombogenic milieu. Segmental infarction typically occurs in the early postoperative period, and prompt diagnosis is difficult to obtain. In view of this, prophylactic heparin may be warranted for those at highest risk. There was no correlation between the infarct area and the graft function, and the long-term graft function is compromised out of proportion to the extent of parenchymal loss. This finding highlights the role of predisposing factors, particularly marginal graft quality, in determining the functional outcome. Segmental infarction may be more frequently encountered as cadaveric organ shortages encourage greater use of marginal donor kidneys.

Keywords: infarction; kidney; renal transplantation

Introduction

In contrast to total graft thrombosis, segmental infarction is uncommonly recognized. Focal perfusion defects following renal transplantation have been the subject of only a few previous reports [1-3]. The incidence in these studies has varied from 4-42%, reflecting heterogeneity in the patient populations and small study numbers. Although an association with rejection, prolonged ischaemia, and multiple renal arteries is reported, the condition remains poorly defined. Recent recognition of segmental infarcts at our institution prompted the present review. This study aims to characterize the clinical manifestations, risk factors, prognosis, and the natural history of this condition.

Methods

A retrospective audit of 13 renal transplant recipients who had segmental infarction at The Queen Elizabeth Hospital, Woodville between January 1997 and January 2000 was performed. The diagnosis of segmental infarction was based on the presence of persistent parenchymal defect on radionuclide renal scan (technetium-99m mercaptoacetylethyl-triglycerine (MAG3) or technetium-99m diethylene triamine pentaacetic acid (DTPA)) and lactate dehydrogenase (LDH) elevation >500 U/l (normal 110-230 U/l). We reviewed
donor characteristics, grafts histology, operative and perioperative course, and medium to long-term follow-up with a mean follow-up period of 14 months (6–27 months). The serial measurement of biochemical changes related to the renal parenchymal necrosis (lactate dehydrogenase, \( \gamma \)-glutamyl transpeptidase (GGT normal 0–60 U/l) and aspartate amino transferase (AST normal 0–45 U/l) were routinely measured starting immediately after the operation and continued daily until the patients were discharged, were also reviewed. Graft segmental nomenclature was described according to the pattern of renal artery segmentation described by Graves and Fine [4]. Delayed graft function was defined as the requirement of maintenance haemodialysis beyond the first 3 postoperative days. Creatinine clearance was calculated by the Cockcroft formula. Pearson analysis was used for evaluation of correlation between variables. Student’s t-test analysis was used for the comparison of graft characteristics and a P-value of < 0.05 was deemed statistically significant.

Results

Segmental infarcts were identified in 13 of 277 transplants (4.7%) performed during this period. The characteristics of donors and recipients are summarized in Table 1. In 11 grafts, radionuclide imaging demonstrated a single wedge-shaped infarct. These extended from the renal cortex to the hilum in a pattern consistent with renal artery segmentation (Figure 1). The lower segment was most frequently involved (five grafts), followed by the upper (three grafts), posterior (two grafts), and anterior-superior segments (one graft). In the remaining two grafts, the lesions were more peripheral. One of these exhibited two separate areas of infarction. Five grafts had two renal arteries. Of these, four developed lesions that correlated anatomically with the occlusion of one artery. In only one patient was an area of focal ischaemia observed at the time of initial reperfusion.

Postoperative Doppler ultrasonography, which was performed routinely in every patient, recognized a segmental perfusion defect in three grafts. Additional imaging with contrast CT scan or magnetic resonance angiography was performed in four patients, each confirming the diagnosis of infarction. Routine biopsy of these lesions was not performed. Five patients who underwent biopsy for suspected rejection demonstrated parenchymal infarction. In addition, the histological diagnosis of segmental infarction was confirmed in one graft, which was removed due to uncontrolled wound sepsis and graft non-function. Follow-up magnetic resonance angiography was performed in three patients, at 1, 5, and 17 months post-transplantation, demonstrating the involution of the involved segment (Figure 2). The pattern of LDH elevation is illustrated in Figure 3. The mean peak LDH level was 931.5 U/l (SD 344.2, range 506–1456 U/l) and LDH levels slowly declined to the preoperative value after a mean period of 29.6 days (SD 14.13). Peak LDH levels did not correlate with the proportion of the infarcted area \((r = –0.79, P = 0.797)\) and the highest creatinine clearance achieved by the grafts \((r = 0.359, P = 0.278)\). GGT elevation occurred in five patients with a mean peak level of 132 U/l (SD 40.0). GGT rose later than the LDH with the mean period of 40.5 h (SD 29.2) and reached a peak level later with the mean period of 36.0 h (SD 13.8).

Elevation of AST was demonstrated in seven patients with a mean peak level of 296.0 U/l (SD 313.0). AST rose and peaked approximately at the same time as LDH (rising, mean 6.2 h, SD 7.9 after LDH, peak mean 0.6 h SD 13.1 before LDH).

The onset of infarction was defined by the commencement of LDH elevation (Figure 3). This could be divided into two groups. Early onset defined as infarction occurred within 24 h postoperatively in nine patients. Late onset, occurred after 24 h (35–245 h postoperatively) and comprised the remaining four patients.

Six grafts in the early onset group demonstrated delayed graft function with initial oliguria (mean first 24 h urine output, 421 ml, SD 439.7) and remained dialysis-dependent for a mean period of 33 days (SD 18.0). Two of these grafts never functioned. These six grafts were also noted to have an immediate rising of LDH in the first hour postoperatively. Two grafts in the early onset group functioned initially but became dialysis-dependent after the onset of infarction. Only one out of four grafts in the late onset group

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**Table 1. General characteristic of the donors and recipients**

<table>
<thead>
<tr>
<th>Recipient [Median age 48 years (range 19–65)]</th>
<th>Donor [Median age 49 years (range 25–73)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes of renal failure</td>
<td>Mean terminal serum creatinine 96 µmol/l (SD 38.0)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>Number and percentage of elderly donor</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>Donor age &gt; 50 years 6 (46%)</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Donor age &gt; 60 years 3 (23%)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Donor sources</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Cadaver donor 11</td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>Living donor 2</td>
</tr>
<tr>
<td>First graft</td>
<td>Cause of death in the cadaver donor group</td>
</tr>
<tr>
<td>Second and third graft</td>
<td>Stroke 8 (61.5%)</td>
</tr>
<tr>
<td>Peak panel antibody &gt; 50%</td>
<td>Trauma, asthmatic arrest, asphyxia one each</td>
</tr>
</tbody>
</table>
demonstrated delayed function. In all six grafts with initial function, the onset of infarction was associated with a plateau or rise in serum creatinine, and decline in urine output (mean reduction from 147 to 27 ml/h, SD 92.1–15.5).

Considering the long-term graft function (Figure 4), excluding the two grafts that never functioned, the mean peak creatinine clearance was 58.5 ml/min (SD 29.5). The peak creatinine clearance was <60 ml/min in six patients. There was no correlation between the proportion of infarcted area and the highest creatinine clearance ($r = 0.04, P = 9.07$). Five grafts were lost and the causes are summarized in Table 2.

Risk factors differed between the early onset and late onset groups, as summarized in Table 3. Major perioperative bleeding was defined as an estimated loss of >1000 ml, a postoperative haemoglobin of <50 g/l or the requirement for >3 U of blood replacement during the first 24 h. This occurred in five patients all of whom developed segmental infarction within 24 h.

Double renal arteries were presented in five grafts. Three cadaver donors had aortic or renal artery aneurysms. Two recipients had calcified atheroma of iliac artery at the site of arterial anastomosis. Insertion biopsies demonstrated moderate to severe arterial hyalinosis in five grafts, scarring of >20% of cortical

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Fig. 1. Radionucleide renal scan. (a) Lower segment infarction, (b) Upper segment infarction, (c) Upper two-third infarction, the lower segment supplied with the patent lower accessory renal artery.

Fig. 2. Magnetic resonance angiography. (a) and (b) Lower segment infarction. (c) Upper segment infarction.

Fig. 3. Pattern of LDH elevation in the early postoperative period. *One patient who had an onset of segmental infarction at 450 h was not included. Early onset, ——; late onset, - - - -.
area in two grafts, glomerular obsolescence of >30% in two grafts, and artheroemboli in three grafts. Pathologic features of tubular damage were demonstrated on insertion biopsies in seven grafts. Both vascular pathology and suboptimal graft pathology occurred more frequently in those with early infarction.

All patients in the late onset group received cyclosporin-based immunotherapy. Two had evidence of cyclosporin toxicity at the onset of infarction based on elevated trough levels (350 and 385 μg/l), graft histology, and requirement of cyclosporin dose reduction. Two further patients in this group received treatment for rejection prior to infarction, comprising pulse methylprednisolone or OKT3. One patient from the late onset group received premarin therapy for intestinal telangiectasia secondary to scleroderma prior to transplantation.

Heparin 4000–5000 IU was administered intraoperatively in six recipients on the basis of multiple arteries, poor initial reperfusion, or operative arterial injury. Three patients developed an early onset of infarction. However, only one patient had an immediate rise of LDH after the operation.

Discussion

The present study reports the clinical characteristics and outcome of renal allograft segmental infarction. The routine use of radionuclide renal scan during the postoperative period in this institution may have contributed to the high detection rate of 4.7%. The onset of segmental infarction was asymptomatic but always associated with impaired allograft function.

In this study, LDH was a retrospective indicator of the onset of infarction. The canine model, a rise in LDH occurred within 1 h of renal artery ligation and the pattern of combined AST and GGT enzymaemia in response to ischaemic injury is similar [5]. In contrast to LDH, neither enzyme is consistently or distinctively elevated. As minor abnormalities in liver function are common after renal transplantation, neither enzyme is a useful adjunct in diagnosis.

In most cases, the morphology of perfusion defects was consistent with occlusion of the segmental artery. Upper and lower pole segments appeared to be over-represented. This may in part be artifactual, reflecting
the superimposition of anterior and posterior segment in the mid-portion on a radionuclide scan. In addition, accessory renal arteries replace a segmental branch, most commonly upper and lower segmental branch, and thrombosis would result in a polar pattern of infarction.

Segmental infarction may share some common aetiology with total graft thrombosis. Both appeared to be multi-factorial [6,7] and the risk factors and timing of onset are similar [7–11].

Anatomical lesions or defect in surgical technique have been identified as a risk factor of total graft thrombosis [7–11]. Pre-existing lesions (atheroma, intimal ulceration, and surgical trauma) in the segmental artery may act as a nidus for thrombus formation in the presence of physiologic thrombogenic milieu. In addition, atheroma may be dislodged during organ perfusion resulting in renal arterial emboli. This may not be apparent during re-perfusion and manifest later after the formation of thrombus over the emboli.

Early segmental infarction was distinctively associated with suboptimal graft quality. Other associated risk factors included operative bleeding and high-peak panel antibody level. Graft tubular damage [9,10] and prolonged ischaemic time [8,9,11] have been identified as the risk factors for total graft thrombosis. Ischaemia induces endothelial thrombogenicity, and graft oedema and diminished perfusion were postulated as the underlying mechanism [8,11]. In addition, high renovascular resistance and a reduction in renal blood flow have been demonstrated in grafts with tubular damage [12]. Interestingly, a segmental pattern of tubular necrosis has also been described in renal allografts [13,14], which may contribute to the pathogenesis of segmental infarction. The high level of panel antibodies has been reported to be the risk factor for total graft thrombosis in the patients without evidence of rejection suggesting the role of antibody-mediated endothelial damage [6,9] as a cause of thrombosis.

In contrast, the late onset of infarction occurred in optimal grafts but seemed to be associated with cyclosporin toxicity and rejection. Cyclosporin has been shown to cause platelet aggregation and inhibition of thrombolyis and a relationship between cyclosporin toxicity and graft thrombosis has been reported. This finding has not been confirmed in other studies [7–9]. The high dose of OKT3 has been associated with total graft thrombosis [15]. The mechanism underlying OKT3 thrombogenicity may be an increase in procoagulant factors 1 and 2 [15].

Genetic predisposition to hypercoagulable state (thrombophilia), such as Factor V Leiden mutation, protein C/S deficiency, the presence of anti-phospholipid antibodies or lupus anti-coagulant, could combine with other risk factors and result in clinical thrombosis [16]. Factor V Leiden mutation carrier state has been implicated as a cause of renal allograft lost in 20% and 4-fold increase in the risk of allograft thrombosis [16]. However, only one patient in this study has been investigated for protein C/S levels and anti-thrombin III antibodies and the results were normal.

The present findings indicate that a finite postoperative interval is required for development of a segmental infarction. This may have a significant therapeutic implication, allowing an opportunity for prophylactic intervention in high-risk patients. Many of the risk factors are known at the time of transplantation including marginal graft quality, significant intraoperative bleeding or haemodynamic compromise, prolonged cold ischaemia, and multiple arteries. The role of heparin in the prevention of graft thrombosis is controversial [17,18] and the potential benefit may be offset by an increase in perioperative bleeding [17]. Heparin appeared to at least delay the onset of infarction in this study. In view of this, we advocate intraoperative heparin for those at highest risk, as the thrombotic potential is greatest in this early period.

As illustrated in this study, complicated recipient surgery may be associated with significant blood loss. Adequate resuscitation must be emphasized, as the graft hypoperfusion was a common risk factor identified in this study and the others [7,10]. Volume resuscitation has been shown to reduce the risk of tubular damage and delayed graft function [19,20], which is a significant risk factor for the segmental infarction.

Where segmental infarction has occurred, conservative treatment is indicated in the majority of patients, particularly if the area involved is small, or diagnosis has been delayed. Contributory aetiopathological factors should be sought and treatment optimized in order to prevent more extensive thrombosis. Appropriate intervention should include maintenance of adequate renal perfusion and effective immunosuppression. Cyclosporin should be avoided where possible, especially in the setting of delayed graft function.

Indications for operative intervention should take into account the interval since onset, infarct size, and arterial anatomy. For successful thrombectomy, early diagnosis is crucial, but in practice this is rarely obtained. Infarction of a single segment should be well tolerated, and the surgery should be reserved for the graft with extensive lesions, where unacceptable loss of graft function is expected. The potential benefit must also be weighed against the associated risks. Re-exploration of a solitary renal artery may jeopardize the remaining viable area, risking total loss of the kidney.

Although some delay in initial function was common, most grafts recovered with suboptimal level of creatinine clearance. Infarcts were typically small, however, and we would predict only a small direct impact on long-term graft function. In most cases, initial graft quality and co-morbidity are more significantly influence graft function. In conclusion, the pathogenesis of segmental infarction may reflect the combination of an initiating anatomic lesion and potentiating thrombogenic milieu. Long-term graft function appears to be compromised. Predisposing conditions, particularly marginal graft quality, seem to
be the major determinant of graft function and final outcome. Segmental infarction typically occurs in the early postoperative period and the prompt diagnosis is difficult to obtain. The use of prophylactic anticoagulation may be warranted for those at highest risk. In an era of cadaveric organ shortage and more widespread use of expanded criterion donors, this entity may be more frequently encountered.

References


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