Acquired Cystic Disease in Chronically Rejected Renal Transplants

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ABSTRACT
Acquired cystic disease has been documented to complicate most forms of chronic renal damage; it has only infrequently been described in transplanted kidneys. Five patients with noncystic ESRD and chronically rejected transplants in which acquired cystic disease arose are reported. The diagnosis of acquired cystic disease was established in examination of transplant nephrectomies from four patients and a core biopsy from the fifth. The allografts were in place from 44 to 80 months; three patients were treated with hemodialysis before the diagnosis of acquired cystic disease, whereas two received peritoneal dialysis. Three of the four patients evaluated had cysts in the native kidneys. Although papillary hyperplasia of lining epithelium was evident in four specimens, only one kidney was the site of neoplasms in the form of multiple small tubular adenomas. No malignant neoplasms were noted in this study or in the few similar previous ones; however, it is possible that chronically rejected transplanted kidneys may harbor neoplasms with the same malignant potential as those in acquired cystic disease in native kidneys.

Key Words: Acquired Cystic disease, chronic transplant rejection, renal cysts

Acquired renal cystic disease, a lesion characterized by the appearance of cysts and neoplasms in kidneys with chronic noncystic damage, has been documented to complicate most forms of advanced structural renal disorders. It is most prominent and expresses its most important features in association with chronic hemodialysis (1). Some investigators have described the regression of cysts in the native kidneys after successful renal transplantation (2), whereas others have suggested that a functioning allograft may retard the development of this lesion in the native kidneys (3). Acquired cystic disease has been infrequently noted in transplanted kidneys with chronic damage due to rejection; we briefly and informally reported this lesion in a single allograft (4), and more recently, Ishikawa and colleagues described a small series of affected patients (5). We report a group of patients with chronically rejected transplants in which acquired cystic disease developed.

MATERIALS AND METHODS
Affected kidneys (either transplant nephrectomies or biopsies) were identified by a retrospective 4-yr review of the files of the Renal Pathology Section at Harbor-UCLA Medical Center; the available reports, slides, and photographs of the specimens were assessed for features of acquired cystic disease. The following features were sought from record review: several visible cortical and/or medullary cysts on gross examination of the transplant nephrectomy or photographs. However, the finding of histologically noted microcystically dilated tubules with or without hyperplastic epithelium was necessary for establishing the diagnosis of acquired cystic disease.

The tissue specimens were processed in the standard manner for light microscopy, electron microscopy, and immunofluorescence (6). Patient charts were reviewed for pertinent information including original renal disease leading to transplantation, duration allograft was in place, serum creatinine at the time of diagnosis of acquired cystic disease, and length of time, if any, of treatment with hemodialysis.
after transplantation. At the time the diagnosis of acquired cystic disease was established, the native intact kidneys of one patient were subjected to ultrasound examination by standard techniques (7).

RESULTS

A total of 510 transplant specimens (417 biopsies, 93 nephrectomies) were evaluated, all microscopically. Chronic rejection was diagnosed in 123 (24%); of these, 5 (4%) from five patients were identified with acquired cystic disease. This diagnosis was established in nephrectomies from four patients and in a core biopsy from one. In no case was this suspected before tissue examination. The patients ranged in age from 10 to 47 yr; three were male, and two were female. The primary renal disease was "idiopathic" focal and segmental glomerulosclerosis in two, reflux nephropathy complicated by focal and segmental sclerosis in one, and obstructive uropathy in the remaining two. The transplants were in place from 44 to 80 months; all patients had received hemodialysis and/or peritoneal dialysis for 2 to 18 months immediately before the diagnosis of acquired cystic disease. Table 1 provides a summary of pertinent data.

Details of the pathological evaluation of the transplant tissues are provided in Table 2. All kidneys had changes of marked chronic rejection, with arterial luminal narrowing and considerable tubular atrophy with interstitial fibrosis. By definition, all had cysts; they were grossly visible in one nephrectomy and were identified microscopically in the other three nephrectomies and single biopsy. The cysts were lined by regular low cuboidal epithelium (Figure 1); in three specimens, concomitant epithelial hyperplasia was present (Figure 2). Neoplasms were evident in only one kidney (patient no. 3) and were discovered microscopically. They consisted of unencapsulated localized collections of closely packed small tubules lined by cells with intensely basophilic cytoplasm and with large, hyperchromatic but regular nuclei (Figure 3).

TABLE 1. Summary of selected clinical features

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Primary Renal Disease</th>
<th>Cysts in Native Kidneys</th>
<th>Duration Allograft in Place (months)</th>
<th>Duration Chronic Renal Failure</th>
<th>Chronic Dialysis Before Diagnosis of Acquired Cystic Disease in Allograft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Female</td>
<td>FSGS</td>
<td>No, bilateral ultrasound</td>
<td>74</td>
<td>20</td>
<td>PD, 2.5</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>Male</td>
<td>Obstructive uropathy</td>
<td>Yes, bilateral bilateral nephrectomy</td>
<td>80</td>
<td>48</td>
<td>HD, 8.0</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>Female</td>
<td>Obstructive uropathy</td>
<td>Not surveyed</td>
<td>72</td>
<td>5</td>
<td>HD, 18.0</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>Male</td>
<td>FSGS</td>
<td>Yes, bilateral autopsy</td>
<td>44</td>
<td>35</td>
<td>HD, 7.0</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>Male</td>
<td>Reflux nephropathy with FSGS</td>
<td>Yes, left surveyed; right, not surveyed</td>
<td>45</td>
<td>48</td>
<td>PD, 2.0</td>
</tr>
</tbody>
</table>

 Abbreviations: FSGS, focal and segmental glomerulosclerosis; HD, hemodialysis; PD, peritoneal dialysis.

TABLE 2. Summary of pertinent renal pathological findings

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of Transplant Specimen</th>
<th>Cysts</th>
<th>Neoplasms</th>
<th>Epithelial Hyperplasia</th>
<th>Other Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nephrectomy</td>
<td>Cortex, medulla</td>
<td>No</td>
<td>No</td>
<td>Transplant glomerulopathy</td>
</tr>
<tr>
<td>2</td>
<td>Nephrectomy</td>
<td>Cortex</td>
<td>No</td>
<td>Yes</td>
<td>Transplant glomerulopathy</td>
</tr>
<tr>
<td>3</td>
<td>Nephrectomy</td>
<td>Cortex, medulla</td>
<td>Yes, multiple</td>
<td>Yes</td>
<td>Transplant glomerulopathy</td>
</tr>
<tr>
<td>4</td>
<td>Core biopsy</td>
<td>Cortex</td>
<td>No</td>
<td>Yes</td>
<td>Transplant glomerulopathy, ATN</td>
</tr>
<tr>
<td>5</td>
<td>Nephrectomy</td>
<td>Cortex</td>
<td>No</td>
<td>Yes</td>
<td>Membranous glomerulonephritis</td>
</tr>
</tbody>
</table>
Acquired Cystic Disease in Renal Transplants

DISCUSSION

This study has documented the occurrence of acquired cystic disease in chronically rejected renal transplants. It extends our earlier informal observation (4) and indicates that damaged parenchyma of allografts may also be "fertile soil" for the development of acquired cystic disease. Only few previous reports have addressed this issue. Our findings complement those of Ishikawa and colleagues (5), who documented acquired cystic disease in transplanted kidneys with chronic rejection by using computerized tomography without contrast enhancement. Four of seven patients evaluated had cysts in allografts, whereas five had cysts in native kidneys. It is of interest to note that, with time, the native kidney cysts increase more in size and number than did those in the transplant.

These results are in contrast to the experience of Vaziri and coworkers who, while assessing the effect of transplants on cysts in native kidneys, did not observe acquired cystic disease in the allografts (3). However, the allografts in all were said to be "functioning," although no measure of renal function was indicated, and the presence or absence of chronic rejection was not noted. Their thesis was that a working transplant can retard the evolution of native kidney acquired cystic disease. In a similar vein, Ishikawa et al. documented the disappearance or diminution of cysts in native kidneys after successful transplantation (2). Fitzpatrick and coworkers assessed long-term allografts for cysts in patients with autosomal dominant polycystic kidney disease (8). Although there was no difference in the incidence of cysts in this and a control group, it is notable that 3 of 10 control patients had allograft cysts. The authors did not comment on their significance, but it is possible that they represent a manifestation of acquired cystic disease.

The stimulus or stimuli responsible for the genesis of cysts and neoplasms in chronically damaged kidneys, whether native or transplanted, is not known (9,10). Although several theories have been proposed, including the suggestion that material from hemodialysis tubing may induce cysts (11), none are wholly

Figure 1. Transplant nephrectomy with severe chronic rejection and end-stage changes and large irregularly contoured cyst with flattened epithelial lining. Note "tributaries" emptying into cyst (arrows) (periodic acid-Schiff; magnification, ×80).

Figure 2. Cyst with small focus of papillary hyperplasia of epithelial cells. There is mild nuclear pleomorphism of the hyperplastic cells (periodic acid-Schiff; magnification ×320).

Figure 3. (A) Small unencapsulated tubular neoplasm in transplant nephrectomy from patient no. 3. This is one of many similar lesions in this kidney (hematoxylin and eosin; magnification, ×160). (B) Note basement membranes surrounding the clusters of neoplastic cells, which are arranged around small lumina, thus indicating them to be tubules (periodic acid-Schiff; magnification, ×320).
satisfactory. It is well known that hemodialysis is not a necessary prerequisite for the development of cysts; patients with chronic renal failure not requiring dialysis have been documented to have cysts (12), and the lesions have been described in patients treated with peritoneal dialysis (13). It has been proposed that obstruction of functioning nephrons, either by oxalate crystals or by hyperplastic lesions or tubular epithelium (14) with proximal cystic dilation of tubules, may be an important factor. Our own observations do not provide new information regarding pathogenesis.

Despite the occurrence of renal cell carcinomas in acquired cystic disease arising in native kidneys, biologically malignant neoplasms have not yet been described in transplants with this lesion. We have documented multiple small tubular neoplasms in only one of our five patients. Ishikawa et al. (5) observed no neoplasms; one patient with "atypical cysts" in the native kidneys did not have these features in an allograft with acquired cysts. It is possible that the development of neoplasms requires a longer period of time than do cysts; because allografts are usually removed when they no longer function, neoplasms and especially malignant tumors may not have sufficient time to arise. However, because chronically rejected nonfunctioning transplants may be left in place, it would be prudent to assess them periodically for the development of cysts or neoplasms.

REFERENCES