Fine-needle Biopsies of Renal Transplants in Clinical Rejection Monitoring

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ABSTRACT

Fine-needle aspiration biopsy (FNAB) of renal allograft transplants has been used at Uppsala University Hospital for 3 years. Experience from 51 consecutive patients (from 1 ½ years) with 333 FNAB was reviewed. Representative material was obtained in more than 70 % of the biopsies. Eleven rejection episodes in 12 patients were confirmed with this method. One was not recognized. Significant inflammation in the kidney without clinical rejection was found in 22 patients. The possible causes of such inflammation are discussed. Repeatedly recorded inflammation in the kidney with minor or no effect on graft function may sometimes be caused by viral infection. The clinical value of FNAB in various immunosuppressive regimens is discussed.

INTRODUCTION

Fine-needle aspiration biopsy (FNAB) as a diagnostic tool in clinical renal transplantation was first reported by Pasternack et al. in 1973 (9), and the method was refined by Häyry & von Willebrand (4). In 1981 Uppsala became one of the first five transplant centres to use this method, which has gained clinical acceptance and currently is used in at least 50 transplant centres throughout the world. Two international workshops have been conducted on the issue (7). Much effort has been devoted to investigating the reliability of FNAB in renal transplants and to refinement of the cytologic diagnosis, e.g. using immune histochemical techniques (3). Less information is available concerning the impact of different immunosuppressive regimens on the method's clinical usefulness.

Instead of comparing FNAB results with the histologic reports, we have related them to the clinical status of the patients. A retrospective review of our own experience is now presented. The impact of immunosuppression with low-dose steroids and cyclosporin or azathioprine on FNAB was studied.

MATERIAL AND METHODS

Patients

The study comprised 51 consecutive patients who had received kidney allo-
graft and were investigated with FNAB during their initial hospital stay. The
immunosuppressive regimen consisted in 18 cases of azathioprine (Imuran[R],
Wellcome, London, UK) and low-dose steroids (Aza) as outlined by McGeown et al.
(8) and 30 patients received Cyclosporin[R] (Sandoz, Basle, Switzerland) and
low-dose steroids (CyA) according to the protocol of the Scandinavian Multi-
center Transplant Study (6). Three patients were switched from one regimen to
the other (Aza/CyA).

Clinical reevaluation

The clinical course was retrospectively reevaluated. A diagnosis of reject-
ion was based on clinical observations of weight gain, fever and pain over the
graft concomitant with rising serum creatinine. In addition, most of the pat-
ients responded with fall of serum creatinine to supplementary steroid treat-
ment.

Fine-needle aspiration

FNAB was performed as described by Häyry & von Willebrand (5). Briefly, a
spinal needle was introduced under sterile conditions into the graft and cells
from this tissue were aspirated into a syringe containing tissue culture medium.
A capillary blood sample was collected at the same time to permit calculation
of a corrected increment.

These biopsies usually were performed at regular intervals (thrice weekly)
during the initial postoperative stay. Some biopsies were performed later, as
need arose.

Table 1. Number of biopsies according to immunosuppressive regimen

Treatment *	No of patients	Total no of FNAB	No of nonrepresent-ative FNAB
CyA	30	190	56
Aza	18	106	31
Aza/CyA	3	37	5
Total	51	333	92

* Definitions in Material and Methods

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Evaluation of FNAB

Cytologic evaluation of the biopsy specimens was performed as previously de-
scribed (11). Essentially this method transposes the observed occurrence of in-
flammatory cells within the graft to a numerical value called the corrected
increment. A corrected increment higher than 2.9 was classified as significant
inflammation. Only biopsies containing 10 or more kidney tissue cells per 100
inflammatory cells were regarded as representative.

RESULTS

Table 1 summarizes the total number of biopsies and the number of nonrepre-
sentative specimens in the three treatment groups. More than 70 per cent of the
biopsies were representative. In this respect there was no clear difference ac-
cording to immunosuppressive regimen. The number of biopsies per patient was
highest in the Aza/CyA group, the reason being that these three patients had a
more difficult and protracted postoperative course than the average.

Table 2. Number of patients with (> 2.9) or without (< 2.9)
inflammation in FNAB at the start of clinical rejection

Treatment	Corrected increment	
	> 2.9	< 2.9
CyA	0	0
Aza	6	3 *
Aza/CyA	2	1 **
Total with rejection	8	4

  * next biopsy positive in 2 of these patients

** next biopsy positive

Table 2 presents the corrected increment in the cases with clinical signs of
rejection. In 11 of the 12 episodes of rejection there was significant rise in
corrected increment. In three patients, however, the increment was below the
significance level (> 2.9) in the morning of the day when rejection started,
but had risen when the next FNAB was taken. For the fourth patient without
significant corrected increment no further FNAB information was available. Not-
ably, there was no rejection episode in the CyA group. The three patients on
Aza/CyA had rejection only when on the Aza regimen.

Table 3. Number of patients and number of FNABs with high corrected increment but without clinical rejection signs

Treatment	No of high increments/patient						No of patients
	1	2	3	4	5	>6	
Aza	4	1		1		2	8
CyA	5	6				1	12
Aza/CyA	1					1	2

The number of high corrected increments (> 2.9) in the absence of rejection signs is shown in Table 3. Altogether 22 of the 51 patients thus had at least one such FNAB but no clinical signs of graft rejection. Retrospective analysis of all these occasions was not within the scope of the present study. However, concomitant cytomegalovirus infection was known from viral isolation or conventional serology to have been present in two of the five patients with at least four high increments. For the other three patients no such information was available.

DISCUSSION

FNAB was equally reliable in patients with CyA and in those with Aza immunosuppression. More than 70 per cent of the routinely performed biopsies yielded representative specimens. This percentage should be improvable with use of ultrasonic guiding, especially if the kidney is difficult to palpate. If a representative specimen is particularly desirable, the probability of success can be increased by making several biopsies. The procedure is in no way harmful to the patient, in our experience or in that from other centres (7). We have performed more than 700 biopsies without complications apart from brief, mild haematuria.

The main advantage of aspiration over "tru-cut" biopsy is, in fact, that FNAB can be performed as often as necessary, thus permitting immunologic monitoring of the patient. The clinical relevance of this monitoring can perhaps be debated. When the Aza immunosuppressive regimen was used, 11 of 12 clinical rejection episodes were diagnosed. Signs of inflammation in the kidney are not pathognomonic for rejection. Thus corrected increments of > 2.9 were often seen without clinical signs of rejection. The reason was not clear, though several explanations may be proposed. First, not all immune reactions to the graft may damage graft function. In addition, subclinical rejection episodes may occur.

Thirdly, virus infections within the graft may cause immune reactions to viral antigens with little effect on kidney function but evoking an inflammatory response. Fourthly, transplantation of organs always induces ischaemic damage to the graft that may lead to some intragraft inflammation. Thus, syngeneic rat allografts are infiltrated with lymphocytes, but the grafts are not rejected (1).

Irrespective of the cause of inflammation observed in FNAB from nonrejecting patients, its frequent occurrence must lead to caution in administering antirejection therapy to patients with high corrected increments unless there are clinical signs of rejection. If high increments are repeatedly found in a patient without clinical signs of rejection, a search for virus infection is advisable (unpublished results). From our total experience of FNAB in Aza-treated patients, it seems warrantable to include these biopsies in the postoperative (first 3 weeks) monitoring of renal transplant patients. If rejection is suspected, at least two biopsies should be performed, if necessary guided by ultrasound scanning, to increase the possibility of a well representative biopsy.

This study demonstrates the rarity of clinical rejection episodes with our present CyA regimen during the postoperative period. Inclusion of FNAB in the routine monitoring of CyA-treated patients is therefore of questionable justification. We shall continue to use the procedure for several reasons, however. Cyclosporin is a nephrotoxic drug and the serum level only partly reflects its toxicity. Some information of the nephrotoxic action can be gained from studying the morphology of the tubular cells in the aspirates (12). As earlier stated, repeatedly high increments have led us to intensify search for viral infections. Use of FNAB should facilitate comparisons with some other, recently suggested monitoring alternatives (2,10).

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