

# Clinical Features in Allografted Patients with Obliterative Angiopathy of the Renal Graft

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Obliterative angiopathy with its unfavourable prognosis and poor response to treatment represents an important problem in organ allotransplantation (Porter et al, 1963; Thomson, 1969). Biopsy of the renal graft makes the diagnosis a relatively easy one; however, one is always rather hesitant to perform biopsy of a single organ, especially if obtained from a living donor, even when it seems that the risks are small (Kincaid-Smith, 1967). Therefore, it seemed worth analysing the clinical picture in patients with this type of lesion and comparing it with that in patients free from it, in a hope that a diagnosis might be established by clinical means only, or at least, that a suspicion based on clinical observation would make the indication for biopsy more justified. Our second aim was to look for factors which might bear some relation to the aetiology and/or pathogenesis of this lesion.

## METHODS AND PATIENTS INVESTIGATED

The study includes 15 patients in whom histological examination of the renal graft was performed one or more months after transplantation. In 7 typical obliterative angiopathy (OA) was found, while in the remaining 8 tubular and interstitial changes with cellular invasion (TIC) without obliterative lesions of arteries and arterioles were present. Relevant personal and clinical data of these subjects are given in Table I; their morphology has been published elsewhere (Rossmann et al, 1970b).

Most of the clinical and chemical methods used were those applied routinely and do not deserve a special comment. Histological diagnosis of the previous renal diseases were made without knowledge of the later course (Jirka et al, 1969), and in the same way transplant crises were assessed retrospectively from clinical and renal functional pattern, using an increase in plasma creatinine concentration of 30 or more percent of its pre-crisis value as a sign of significant change in renal function. The functional reversibility of the crises was judged by whether creatininaemia returned to

Table I. Relevant personal and clinical data of patients studied

Patient	Sex	Age	Previous disease	Donor	HLA-antigen difference	Tissue specimen obtained by	Time after transplant	Indication for biopsy
Patients with obliterative angiopathy								
KP	M	24	Polycystic disease, GNC	mother, 49	0/10	Nephrectomy	36	-
PS	M	21	GNC	brother, 24	0/6	Biopsy	2	Rejection crisis
PC	M	26	GNC	father, 56	3/10	Biopsy	1	Rejection crisis
VR	M	24	GNC	mother, 57	2/6	Biopsy	11	Renal failure
ZH	F	26	GNC	father, 60	3/7	Necropsy	20	-
KS	M	34	GNC	father, 62	0/6	Necropsy	17	-
JP	M	18	GNC	mother, 44	2/9	Nephrectomy	8	-
Patients with interstitial and tubular lesions								
AG	F	29	GNC	sister, 39	0/7	Biopsy	2	Rejection crisis
ID	F	18	GNC	mother, 43	1/7	Biopsy	16	Haematuria
PL	M	23	GNC	mother, 50	1/9	Biopsy	3	Nephrotic syndrome
DR	F	27	PNC	mother, 49	0/6	Biopsy	12	Rejection crisis
PZ	M	22	PNC	mother, 43	1/9	Biopsy	10	Rejection crisis
JK	M	21	uncertain*	cadaver, 18	1/10	Biopsy	6	Rejection crisis
JU	F	26	uncertain**	father, 55	0/9	Biopsy	10	Rejection crisis
AS	M	39	uncertain*	cadaver, 38	?	Biopsy	4	Post-rejection control

GNC = chronic glomerulonephritis. PNC = chronic pyelonephritis

\*not nephrectomised. \*\*no agreement about diagnosis

The second number in the HLA-antigen difference column is number of antigens determined

Table II. Data in which at least some difference was found between OA and ITC groups

Group	Plasma Proteins (g/100 ml, mean)	Hypertension (number of cases)	Definite rejection (number of cases)	C <sub>cr</sub> at the time of histology (ml/min, mean)	Rejection crises first trimester total	Rejection crises prior to biopsy
OA	4.62 ± 1.10	5	6	25.63 ± 25.68	17	11
ITC	6.11 ± 0.37	1	0	47.25 ± 18.01	9	3
	P < 0.005	< 0.05	< 0.005	0.05 < p < 0.10	< 0.01	N.S.

< 0.025

OA = obliterative angiopathy group. ITC = interstitial and tubular lesions with cellular invasion

Rejection crises prolonged = lasting 14 days and more

N.S. = not significant

the pre-crisis value (or at least did not remain persistently elevated by more than 10%), and their duration estimated from the interval between the last pre-crisis and the first stabilised post-crisis value; histocompatibility was tested by leucocyte typing using the agglutination method of Dausset. The differences between both groups of patients were tested for statistical significance by usual methods.

## RESULTS

Table II shows the clinical data in which there was at least some difference between the two groups studied. No significant differences were found in the mean proteinuria, number of elements in urinary sediment, ESR, haemoglobin and plasma cholesterol concentrations and in electrophoretic pattern of plasma proteins; therefore these values are not published. The same applies to the mean age of donors, to the interval between transplantation and the time when biopsy was performed, and to the degree of functional involvement during rejection crises and their functional reversibility.

From the table it is evident that there was a lower mean plasma protein level, a higher incidence of persistent and recurrent hypertension, a slightly lower mean creatinine clearance at the time of biopsy, more definite rejection episodes, and more frequent rejection crises both in the first three months and before biopsy in the angiopathy group.

## DISCUSSION

The results of this comparative study show that in our patients with obliterative angiopathy no clear-cut clinical pattern was present which could be considered diagnostic. However, there were several features which are strongly suggestive and which should arouse suspicion. The most important seems to be a persistence or recurrence of diastolic hypertension. In a group of 14 patients with renal allografts and bilateral nephrectomy, followed for at least 6 months after transplantation, we found that their mean weekly blood pressures decreased below 150/95 mm Hg on average before the end of the first trimester in all but one: in this patient obliterative angiopathy was found by biopsy performed 55 days after grafting (Jirka et al, 1970). In the present study hypertension persisted in two and reappeared in three out of seven patients with angiopathy, while it did not persist in any and recurred only in one out of eight subjects without angiopathy. While in the former it persisted in the presence of satisfactory function of the graft ( $C_{cr}$  62 ml/min, subject PS, Table I) and reappeared in two at the time when their creatinine clearances were 60-70 ml/min, in the latter its reappearance in the single case did not occur before the creatinine clearance had decreased to 30 ml/min in consequence of recurrent glomerulonephritis (Rossmann et al, 1970a).

We did not confirm either the observations of Porter et al (1963) who had

found proteinuria exceeding 1.0 g/24 hr in all their four patients with angiopathy, or the experience of Dempster et al (1963) who had observed unexplained fever in five out of their seven patients. In our patients with vascular lesions proteinuria ranged from 0.2 to 9.0 g/day, but the mean value 1.8 did not differ significantly from 0.5 g/day in the other group; as for febrile episodes, they were equally frequent at the time of crises in both groups and persistent fever was not encountered.

The cause of the depressed plasma protein levels in patients with angiopathy is not clear; as already mentioned their mean loss of protein in urine was not higher, and only one patient showed the full biochemical picture of the nephrotic syndrome. Although we did not find any correlation between plasma protein and creatinine clearance, the most probable explanation seems to be the fact that in most patients angiopathy was confirmed when irreversible renal failure was already present.

The lower mean creatinine clearance at the time of biopsy in patients with angiopathy, together with definite rejection of 6 out of 7 allografts reflect progressive reduction of renal function and poor prognosis for the grafts. Renal failure due to definite irreversible rejection occurred in two patients at 6 months and in the remaining four 7, 11, 20 and 36 months after transplantation. The last patient died in a country hospital of intercurrent bronchopneumonia in the 17th month; during his illness his plasma creatinine was 4.2 mg/100 ml, so it is most probable that his graft was failing as well. In patients free from angiopathy (living now 7 to 32 months after grafting) there has not been a single case with definite rejection, and in the latter of the two subjects in whom the creatinine clearance decreased below 30 ml/min 12 and 24 months after transplantation extracapillary glomerulonephritis was found.

Our observation that patients with vascular lesions showed more frequent and protracted rejection crises is similar to that of Kincaid-Smith (1967); in several of our patients these crises followed in such quick succession that it was sometimes very difficult to differentiate one from another. As for the clinical features of these crises, they did not differ from those in patients without angiopathy. Thus, our experience is in agreement with that of Porter et al (1963) and in contradiction to that of Dempster et al (1964) who had observed symptomless development of vascular lesions in their patients. In the first trimester both groups did not differ significantly in functional reversibility of these crises after anti-rejection treatment (13 out of 17 in OA vs 8 out of 10 crises in ITC group) and in one subject a marked improvement of vascular changes was found in a follow-up biopsy carried out after treatment with prednisone and ALG.

As for possible pathogenetic factors, hypertension in the recipient, more frequent rejection crises and previous renal disease seem to deserve discussion.

In two of our patients angiopathy was diagnosed by histology when normal blood pressures were present, so that more probably hypertension is a consequence and not the cause of this lesion, as suggested already by Porter et al (1963) and Kincaid-Smith (1964). The significance of frequent rejection crises for the pathogenesis of vascular lesions is not clear. Dunea et al (1964) believed vascular lesions to be a consequence of preceding crises, but Kincaid-Smith (1964) found that vascular changes may precede any clinical manifestations of rejection. As regards the relation between vascular and interstitial lesions, Hamburger (1967) did not observe any correlation between cellular infiltration and late angiopathy, and in the present series there was not a single case in the angiopathy group in which pure interstitial lesions had preceded the vascular ones in repeated biopsies (5 subjects); therefore it seems that lesions of purely interstitial cellular type do not develop vascular changes and that both represent two separate entities from the beginning. Thus, the higher frequency of crises would be a sign of a more intense immune reaction of which angiopathy is undoubtedly a morphological consequence (Porter et al, 1963). This view is supported by the fact that in four out of the seven subjects with vascular lesions differences in more HLA antigens were present than in any of the patients of the other group, even though our patients are not fully comparable in this respect due to different numbers of antigens being determined.

In all our patients with angiopathy glomerulonephritis had been the primary disease, while it had been so with certainty in only 3 out of 8 patients of the other group. This is most probably due to a coincidence since no relationship between angiopathy and the type of previous disease has yet been reported and, on the contrary, in most of the patients of Porter et al (1963) and of Dempster et al (1964) pyelonephritis was the cause of chronic renal failure.

#### SUMMARY

1. The clinical pattern in 7 patients with vascular lesions and in 8 patients with interstitial and tubular lesions in their renal allografts were compared in an attempt to make a clinical diagnosis of the former more reliable, and to look for factors which might play a role in the pathogenesis of this type of lesion.
2. No clear-cut pattern was found which would make it possible to diagnose angiopathy by clinical means only. However, the patients with this type of lesion displayed a higher incidence of hypertension, lower plasma protein levels, progressive deterioration of renal function, a higher incidence of definite rejection episodes and more frequent rejection crises in comparison with patients with interstitial and tubular nephropathy.
3. The significance of these observations for the diagnosis and pathogenesis of angiopathy are discussed.

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Due to the absence of Dr Reneltová only the abstract was available at the Conference