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Protracted Anuria Due to Active Vasoconstriction in Primary or Secondary Malignant Hypertension

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Abstract. Anuria complicated the malignant phase of hypertension in twelve patients (ten males and two females). Five were black; five had primary hypertension; one had HBs virus angiitis; the six remaining cases suffered from previously documented renal disease, including two with Berger's disease. Renal angiography showed interruption of renal blood flow as far as the main branches of the renal artery and/or a false impression of 'cortical necrosis' and of 'renal infarcts'. In contrast, renal biopsy did not show irreversible vascular damage. Thus, anuria was mainly functional and due to active renal vasoconstriction. This was confirmed by the subsequent course; diuresis resumed after 1 week to 24 months of dialysis. Repeat angiography in six cases showed recovery of renal circulation and disappearance of 'cortical infarcts', even when plasma renin activity remained elevated and hypertension was not controlled. In one case captopril induced a new reversible episode of anuria. These observations suggest that active vasoconstriction with prolonged anuria might be due to some vasoconstrictive substance other than angiotensin II.

Key words: Malignant hypertension; Anuria; Angiography (renal)

Introduction

Acute anuria, or rapidly progressive renal failure, often accompanied by microangiopathic anaemia and haemostatic disorders, are known features of malignant hypertension. Angiography reveals profound impairment of renal perfusion and sometimes cortical necrosis [1]. The belief that the anuria of malignant hypertension is definitive was reconsidered when recovery of renal function was reported after a long period of haemodialysis [2–4]. In a few patients angiography was performed at the onset of anuria and showed severe cortical ischaemia [5–10]. The pathophysiology of such prolonged renal shutdown in malignant hypertension is poorly understood, and repeat arteriography has very rarely been performed after resumption of diuresis.

We have observed 12 cases of severe renal failure complicating malignant hypertension. One was followed up before the onset of hypertension, during three periods of anuria (the last being induced by captopril), and after discontinuation of haemodialysis. In eight, angiography was performed during the period of anuria and in six repeat angiography was done after dialysis had been stopped. Renal histology was examined at the same stages. It appeared that anuria was mostly due to active renal vasoconstriction. These observations illustrate a mode of renal failure which does not find a place in the simple classification into 'acute' versus 'chronic' and 'organic' versus 'functional' renal failure.

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Case Reports

Demographic Data

The main features of the 12 patients are summarised in Table 1. There were ten males and two females, aged 24–57 years. Six were black. Past histories revealed that two had already been followed up for long-standing hypertension. One of them was also addicted to intravenous illicit drugs and the onset of malignant hypertension coincided with HBs virus infection. Five patients were already being followed up for renal disease: one had scleroderma; five had previously undergone renal biopsy, which had disclosed membranous glomerulopathy in one and IgA nephropathy in two. In the remaining two renal biopsy had shown vascular lesions interpreted as 'benign nephrosclerosis'. Of the remaining five, one was on combined oestrogen-progesterone contraception, one had anticardiolipin antibodies, and the others had no relevant medical history.

Clinical

The presenting features were the sudden onset of malignant hypertension in seven and rapid aggravation of pre-existing hypertension in five, which in one coincided with discontinuation of previous treatment. Systolic BP was (range, mmHg) 180–270, diastolic BP was 110–170, funduscopy showed (K & W) grade III in five patients and grade IV in seven. Nine patients had microangiopathic anaemia. Eight were anuric. Serum creatinine was 540–2024 μmol/l.

Angiography

In seven of eight cases angiography disclosed disappearance of cortical circulation. In one the contrast medium did not progress further than the segmental arteries (Fig. 1). An aspect of pseudocortical necrosis with the appearance of multiple renal infarcts was seen in three cases. One patient with documented membranous GN also had stenosis of the right renal artery.

Renal Lesions

Percutaneous renal biopsy was carried out in nine patients. In four histology disclosed renal lesions (glomerular in two and vascular in two, as specified above). In the nine patients the lesions which could be responsible for acute renal insufficiency were glomerular and arteriolar lesions of thrombotic microangiopathy in two, tubular necrosis in one and malignant nephrosclerosis in four, including a case with scleroderma. In the remaining two benign nephrosclerosis was present, but nothing in renal histology clearly explained why the patient was oligoanuric.

Evolution

All patients were treated with high doses of frusemide upon admission. Combined antihypertensive therapy was begun, with angiotensin II converting enzyme inhibitors in ten, beta-blockers in eight, minoxidil in six, dihydralazine in four, calcium-channel antagonists in three, diazoxide in two, clonidine in two and prazosin in one. Haemodialysis was begun in 11 and peritoneal dialysis in one.

Progressive increase in urinary output allowed discontinuation of dialysis within 1 week to 30 months. By the end of the dialysis period, serum creatinine was (range) 205–520 μmol/l and creatinine clearance was 16–52 ml/min. Repeat angiography was done in six cases. In four renal circulation was strikingly improved (Fig. 2). In one angiography revealed a small left kidney and a right renal-artery stenosis. In the last case angiography showed persistent cortical ischaemia. Repeat renal biopsy was done in six cases. In three the overall aspect was not substantially modified as compared with first biopsy findings. Of the remaining three one had disappearance of glomerular thrombosis, in one severe endarteritis lesions had improved, and in one benign nephrosclerosis was still present. In three cases, (nos 1, 3 and 9 in Table 1) plasma renin activity was still high when diuresis resumed.

Follow-up was 3 months to 11 years. In nine cases renal function remained sufficient to sustain life without dialysis. In three subsequent progression of renal failure was observed and dialysis was resumed. In all, heavy antihypertensive therapy had to be maintained.

Discussion

Malignant hypertension may complicate primary hypertension, chronic renal disease, scleroderma [11] or angiitis [12]. It may also occur in patients whose blood pressure and renal function were previously normal, especially in blacks [13]. It was shown that the severity of vascular damage has a bearing on the long-term outcome of acute renal failure [14]. Histology shows fibrinoid necrosis of arterioles, proliferative endarteritis of interlobular arteries, ischaemic glomeruli and tubular atrophy. When cortical necrosis is present, renal failure is not expected to regress. The usual evolution during maintenance haemodialysis is characterised by persistence of severe hypertension with high plasma renin activity. Until efficient antihypertensive drugs were available, bilateral nephrectomy was often mandatory [15,18]. Beta blockers, minoxidil and angiotensin II converting enzyme inhibitors have made this extreme procedure unnecessary [5,6].

That a patient with malignant hypertension and anuria can eventually discontinue haemodialysis has been documented since 1971 in 17 reports, totalling 44 cases [2–10,16,17,19–23] with a predominance of blacks. Ages ranged from 11 to 61 years with a majority in their 3rd and 4th decades. In all but five [6,20–22], acute renal failure occurred in persons whose previous renal function was

Table 1. Main demographic features in twelve cases of severe renal failure complicating malignant hypertension

Patient no.	Age (yrs)	Sex	Race	Funduscopy (K & W)	Microangio-pathic anaemia	Anuria or severe oliguria	Serum creatinine (μmol/l)	Initial renal angiographic appearance	Initial renal biopsy	Duration of dialysis	Repeat angiography	Repeat renal biopsy	Last serum creatinine	Duration of follow-up
1	27	M	B	IV	+	+	> 1000	'Cortical ischaemia & necrosis'	Glomerular & tubular ischaemia; severe endarteritis	3 mo	Improved cortical perfusion	Disappearance of endarteritis	166	11 yrs
2	41	M	B	III	+	+	> 1000	ND	ND	12 mo	Cortical ischaemia	Nephro-sclerosis	520	1 yr, then ret. to HD
3	31	M	B	III	+	+	> 1000	'Cortical ischaemia & necrosis'	ND	2 mo	Improved cortical perfusion	ND	205	2 yrs, then ret. to HD
4	43	M	B	IV	+	+	> 1000	Cortical ischaemia	'Malignant nephro-sclerosis'	2 mo	ND	Unchanged	180	6 yrs
5	30	M	W	IV	+	+	540	Cortical ischaemia & 'renal infarcts'	Tubulo-interstitial lesions	3 mo	Improved cortical perfusion	Unchanged	160	4 yrs
6	27	M	W	IV	–	+	> 1000	ND	Berger's disease Nephro-sclerosis	9 mo	ND	Unchanged	450	1 yr
7	27	F	W	III	+	+	> 1000	Two small ischaemic kidneys	Thrombotic micro-angiopathy	2.5 yrs	ND	ND	390	7 mo
8	57	M	W	III	+	+	> 1000	Cortical ischaemia	Vascular lesions of scleroderma	2 yrs	ND	ND	362	7 mo
9	47	M	W	III	–	–	> 1000	ND	ND (Previous biopsy showed membranous GN)	2.5 yrs	Small left kidney; stenosis of right renal artery	ND	250	1 yr
10	28	M	B	IV	+	–	> 1000	Cortical ischaemia	Malignant nephro-sclerosis	3 mo	ND	ND	380	8 mo, then ret. to HD
11	24	F	W	IV	+	–	850	Minor alterations	Thrombotic micro-angiopathy	1.5 mo	ND	Disappearance of most lesions	240	3 mo
12	31	M	W	IV	–	–	> 1000	ND	Berger's disease Malignant nephro-sclerosis	1 wk	Normal cortical perfusion	ND	450	4 mo

M, male; F, female; B, black; W, white; ND, not done; yrs; years; mo, months; HD, haemodialysis

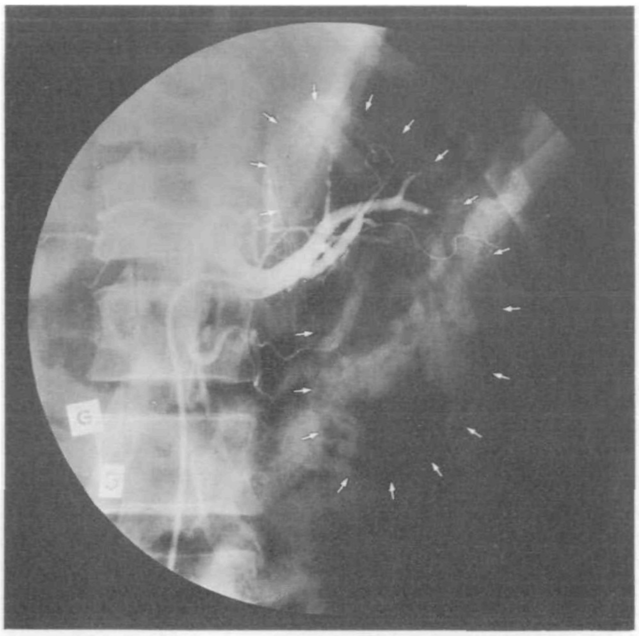

Fig. 1. Twenty-seven-year-old black male with no relevant medical history and in whom recent blood pressure measurement had been 120/90 mmHg. This renal angiography was carried out 4 days after onset of malignant hypertension and anuria. The size of the kidneys was normal (kidney outline is indicated by arrows). Anuria was obviously due to active renal vasoconstriction: the contrast medium opacified only the trunk and the main branches of the renal artery and blood did not progress further. Note the beaded appearance of the artery directed toward the upper pole.

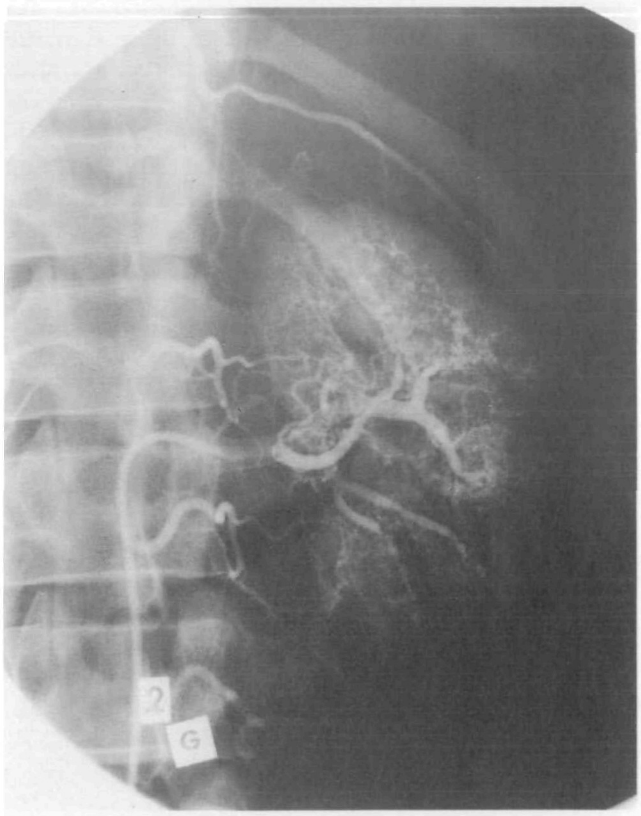

Fig. 2. Same patient. Diuresis resumed after a protracted period of severe oliguria which had necessitated 6 months of dialysis. At that time blood pressure was 140/100 mmHg and serum creatinine was 600 µmol/l. Selective arteriography now disclosed reappearance of renal circulation which progressed almost down to the cortex, although the small-calibre renal arteries had a markedly abnormal appearance. At this time plasma renin activity was still extremely high. Renal angiography was immediately followed by a second episode of anuria and the patient was returned to haemodialysis for 9 months. Follow-up is 9 years since last dialysis.

presumably normal. In 70%, hypertension had been diagnosed 1–13 years earlier and had usually been neglected. Three patients had scleroderma [20–22]. In 23, renal biopsy performed in the anuric phase showed malignant nephrosclerosis in 19 [2,3,5–8,10,16,17,20,22]. Angiography, performed in only eight cases [5,6,8–10,18,21] disclosed cortical ischaemia in four. In most cases improvement of renal function followed BP control by beta blockers and/or vasodilators, especially minoxidil, which was used in 18 patients [3–6,10,16,19,21,23]. In one case [6] renal function resumed after 9 months, despite persistence of uncontrolled hypertension. Duration of maintenance haemodialysis was 1–25 months. Follow-up after discontinuation of haemodialysis was 1–50 months. Last GFR reported ranged from 4 to 41 ml/mn.

Few of these reports afford any insight into the mechanism of protracted anuria. In only two cases [6,17] was repeat angiography done. It is difficult to know whether amelioration of renal function was due to improvement of vascular lesions [24], or to regression of vasoconstriction. Likewise, histological data are scarce. Isles et al [16] have ascribed resumption of diuresis to healing of tubular necrosis. They considered that such acute tubular lesions, following malignant hypertension with vascular lesions of rapid onset, entailed a better prognosis than when arteriolar lesions develop more slowly.

Our cases shed some additional light on the sequence of events in transient anuria associated with malignant hypertension. Initial arteriography mostly showed extreme vasoconstriction. After diuresis had resumed, the angiographic appearance was still very abnormal, but the radiological interpretation as 'severe endarteritis' was excluded by histology. We did not find acute tubular necrosis except in one case. This lesion was still present when dialysis was stopped.

This syndrome does not fit with the classical distinction between 'organic' and 'functional', or 'acute' and 'chronic' renal failure. The picture is that of functional, rather than organic renal shutdown due to active renal vasoconstriction, and recalls some features of functional renal failure of cirrhosis. In anuric cirrhotics Epstein et al [25] demonstrated a profound decrease in cortical perfusion, whereas post-mortem angiography disclosed a normal vascular bed. Kidneys of cirrhotic patients who died with extreme degrees of functional renal failure resumed subnormal function after being used for transplantation [26]. The major difference between cirrhotics and our patients is that the former have normal blood pressure, but in our cases, as in the hepatorenal syndrome, the nature of the vasoconstrictive substance is by no means evident. Clinical and experimental data do not support the role of increased sympathetic activity, despite similarities with experimental renal failure elicited by noradrenaline infusion [25,27]. The role of angiotensin II could be only partial, as radioimmunoassay still revealed greatly elevated renin concentrations at a time when diuresis had resumed and renal angiography showed open arterioles. Moreover, in a number of other clinical situations massive renin secretion is not associated with renal failure, and converting enzyme inhibitors may induce anuria, as captopril did in one of our patients.

Recently, Yanagisawa et al [28] isolated an endothelial peptide, endothelin, which seems to be the most potent vasoconstrictive substance presently known. Firth et al [29] discussed the role of endothelin in acute renal failure. In the haemolytic–uraemic syndrome, endothelin release could elicit extreme renal vasoconstriction. We are tempted to speculate that endothelin release might also explain some of our findings.

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