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PATHOLOGY OF BALKAN ENDEMIC NEPHROPATHY – A CORRELATION WITH ESTABLISHED KIDNEY DISEASE ENTITIES

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Summary. *The aim of the paper was to summarize the results of autopsy studies of end-stage Balkan endemic nephropathy (BEN), to compare the results of our biopsy studies of earlier stages with those of other research groups and to discuss the issue of the most up-to-date hypothesis about the pathogenesis of this still enigmatic disease. Our experiences have been based on light microscopic examination of 12 end-stage autopsy cases, 4 nephrectomies from patients from endemic areas with urothelial upper urinary tract tumors and a systematic study by light, immunofluorescence and electron microscopy techniques of strictly selected kidney biopsies from 50 patients with earlier stages of BEN. End-stage pathology is characterized by extremely small sized, smoothly surfaced contracted kidneys, showing a peculiar cortical histotopography of sclerosing atrophy and frequent association with urothelial upper urinary tract tumors. Characteristically pronounced condensation of sclerosing atrophy of all nephron compartments, particularly tubulo-interstitial, in the outer subcapsular cortex is similar to that of Chinese herbs nephropathy and vascular nephrosclerosis. Multifocal chronic inactive sclerosing non-specific lesions regularly found in the kidneys of earlier stages of BEN may suggest accelerated ageing triggered by long-lasting low-dose exposure to an unknown environmental nephrotoxic and mutagenic agent similar to ochratoxin A and aristolochic acid. Significantly less extensive but not infrequent additional biopsy findings, sharing similarities with the histopathology of chronic cyclosporine nephrotoxicity, indicate endothelial cells of small intrarenal blood vessels to be an important target in the pathogenesis of BEN.*

Key words: *Balkan endemic nephropathy, pathology, electron microscopy, etiopathogenesis*

Introduction

End-stage Balkan endemic nephropathy (BEN) has been fairly extensively investigated in the past by several research groups from different endemic areas. A limited number of biopsy studies of earlier stages were carried out with a delay, during the seventies and eighties, only exceptionally systematically, introducing all modern techniques, unfortunately with no biopsy follow-up to date.

The aim of this paper is to present our experiences with the pathology of early and advanced BEN in view of autopsy and biopsy findings by other groups and the comparable pathology of some well-established kidney disease entities.

Material and Methods

Our experiences have been based on light microscopic examination of 12 end-stage autopsy cases, gross and microscopic examination of 4 nephrectomies from patients with upper urinary tract tumors and more than 100 percutaneous needle and, occasionally, surgical biopsies in patients with earlier stages of BEN assessed by traditional light microscopical methods on formalin-fixed and paraffin embedded specimens and, additionally, by immunofluorescence technique on frozen tissue as already previously described (1,2). By taking into account very strict diagnostic criteria, 50 biopsy cases were selected for semi-quantitative evaluation and comparison with 50 kidney tissue specimens of an age-matched control group. Electron microscopic study was performed on 15 percutaneous needle kidney biopsies of patients with early BEN. The statistical analysis included the nonparametric χ^2 test for comparison of the principal histomorphological renal changes between BEN and control groups.

Results and Discussion

Autopsy studies provided data about the pathology of end-stage BEN, as well as of the peculiar histotopography of the basic lesions. Biopsy studies, despite several limitations, provided some evidence about the his-

topathology of earlier stages and enabled comparison with well-established kidney disease entities and discussion of the etiology. Data on the histomorphogenesis of BEN are still missing because of a complete lack of systematic biopsy follow-up studies.

Autopsy Studies and Histotopography of Basic Lesions

Most of the autopsy studies from different endemic areas already performed in the pre-dialysis era gave a fairly uniform gross description of end-stage BEN kidneys: bilaterally and symmetrically contracted kidneys of a very small size and a reduced weight by up to 40 grams, with a smooth, only mildly undulated, rarely slightly granular surface, and very prominent reduction of the cortical thickness to 0.5 – 2 mm but fairly well preserved medulla with no papillary necrosis on the cut surface (3-8). Similarly to our limited observation, coincidental solitary or multiple, unilateral or bilateral upper urinary tract papillary tumors were demonstrated in 8 - 48.4% autopsied patients (cited in 8). On the basis of such characteristic gross appearance, the contracted kidneys from end-stage BEN patients can usually be distinguished from well-recognized glomerulonephritic, pyelonephritic and arterio-arteriolosclerotic nephrosclerosis, and occasional differences in macroscopical appearance were ascribed to coincidental other diseases (8).

Although classical descriptions of the basic histomorphological changes in autopsy specimens of the kidney were fairly concordant, the interpretation of the etiopathogenesis and morphogenesis by different authors occasionally varied significantly (8,9): marked hypocellular interstitial fibrosis/sclerosis, tubular atrophy and vanishing, cellular interstitial infiltration of variable intensity and localization, never massive, preserved or sclerosed glomeruli usually of collapsing obsolescence, sclerotic changes on blood vessels, a frequent association with transitional cell papillary upper urinary tract tumors. Occasionally observed irregular massive destructive interstitial inflammatory infiltration, mixed cell or mononuclear, sometimes forming lymph follicles (3,6), have probably to be ascribed to pyelonephritis (10), in some studies a fairly frequent coincidental finding in BEN patients (11). There are no firm arguments that cell-mediated hypersensitivity might be involved in the development of BEN, as suggested by some authors (12). It has been concluded by several authors that BEN is one of the non-destructive, non-inflammatory and non-specific tubulo-interstitial renal diseases with unelucidated etiopathogenesis (8).

The etiology is difficult to elucidate on the basis of post mortem material or morphology in general, and some authors even completely deny the diagnostic value of autopsy material because the advanced sclerosing process with possible secondary changes may mask completely the underlying disease. Nevertheless, the final stages of various renal diseases may still differ according to some more or less prominent residual changes and preserved peculiarities.

A peculiar quantitative histotopography of the basic lesions is a striking feature, found to be consistent with gross descriptions at autopsies and already pointed out by several authors. Not in all cases diffuse and expressed to the same extent, but generally, the external cortical subcapsular zone in the kidneys of BEN patients is affected by hypocellular interstitial fibrosis and condensed sclerosing atrophy of all nephron structures much more severely than intermediate and juxtamedullary inner cortical zones (3,5,7-10,13,14).

Histotopographic quantitative differences in cortical sclerosing atrophy was confirmed and particularly stressed by our evaluation, not only at autopsy but also on biopsy kidney tissue specimens, which suggests their occurrence in early stages, their accentuation during the progression of the disease, and their preservation at the end-stage (1,15).

Knowledge of the histotopography of pathological changes in kidney diseases is scanty. More or less widespread tubular atrophy and interstitial fibrosis is a well known consequence of global glomerular sclerosis occurring in various forms of sclerosing glomerulonephritis. The progression of focal glomerulosclerosis, also termed focal sclerosing glomerulonephritis, occurring in the context of idiopathic nephrotic syndrome, seems to be related to hyperfiltration/hyperperfusion glomerular injury which, in contrast to BEN, involves primarily and predominantly the juxtamedullary cortex. In contrast, Zollinger and Mihatsch (16) report that in all cases of arteriolosclerotic vascular atrophy, changes are most prominent in subcapsular parts of the renal cortex. The sclerosing process, predominantly involving the superficial cortex, has accordingly been described as a consequence of ischemic injury, secondary to vascular sclerosis (17). A similar histotopographic distribution of sclerosing atrophy as in BEN has also been observed in chronic vascular rejection of kidney transplant and, particularly, in recently discovered Chinese herbs nephropathy, obviously caused by contamination of Chinese pills for a slimming regimen with nephrotoxic and mutagenic aristolochic acid from the widely growing weed, Aristolochia clematitis (18). It has to be stressed that similar vascular changes, which will be discussed later, have been commonly observed in both Balkan endemic nephropathy (1,8) and Chinese herbs nephropathy (18). A relative preservation of the renal tissue in the Bertin's columns was found in BEN by only some authors (13,14) and not confirmed in our study of BEN, nor pointed out in the study of Chinese herbs nephropathy (18).

BEN has already been widely accepted as an environmental polytopical disease of the entire urinary tract in which, in addition to chronic progressive nephropathy, mostly defined as chronic non-destructive tubulo-interstitial nephritis, urinary tumors, especially transitional cell papillary carcinoma of the renal pelvis and ureter, represent constituents of this unique nosological entity (19). A common, well-established renal disease in humans, termed analgesic nephropathy, shares similarities with BEN. About 10% of analgesic abusers have

been found to have upper urinary tract transitional cell papillary tumors (20). This figure is about 10 times higher in analgesic abusers and up to 100 times higher in BEN endemic areas than that found in autopsy controls from non-endemic areas (21). A picture of chronic non-destructive tubulo-interstitial nephritis with interstitial sclerosis and tubular atrophy, similar to that in BEN, is limited to the cortex. Nevertheless, while in analgesic nephropathy, the inner renal medulla is typically affected by papillary necrosis followed by characteristic scarring, calcification and ossification in the surrounding of mutilated areas, in BEN patients it is relatively preserved. The scarring in analgesic nephropathy usually spares the cortical column of Bertin which, due to richer vascularization by numerous anastomoses, responds more weakly to circulatory disorders than the cortex (22).

Biopsy Studies and Tentative Etiopathogenesis of BEN

Tubulo-interstitial changes were the most prevalent in our series of 50 kidney biopsies obtained from preuremic, mostly pre-azotemic early BEN patients, occurring significantly more frequently and on average in a significantly more extensive form than in the age-matched control group (Table 1). Interstitial fibrosis was characteristically hypocellular, mostly scattered, in surgical wedge-shaped biopsies evidently more pronounced and multifocal confluent in the subcapsular outer zone of the cortex. It was found accompanied by multifocal tubular atrophy, usually of collapse type, occasionally simple and rarely dilatative. More than 25% tubulo-interstitial involvement was found in the BEN group only.

Statistically, multifocal global glomerulosclerosis, arteriolosclerohyalinosis as well as arterial intimal fibroelastosis were also more frequent and more extensive in BEN patients than in the age-matched control group (Table 1).

Taking into account only these chronic inactive, usually multifocal sclerotic and atrophic changes involving all nephron compartments, by far the most frequent and extensive lesions found in our biopsy study of early BEN, no qualitative but significant quantitative differences were found between the early BEN patient group and the age-matched control group (Table 1).

In general, sclerotic lesions in the kidney are a non-specific terminal consequence of irreversible injury of a variable etiopathogenesis. To a certain extent, they may occur without any clinical signs of a disease in a normal ageing kidney, but can occasionally be found even in very young children. Glomerular and vascular sclerosis, as well as interstitial hypocellular fibrosis, accompanied by tubular atrophy, are known to develop at an increasing incidence and severity with age (17,23-27). These chronic inactive histological changes involving multifocally, simultaneously or consequentially all nephron compartments have already been included in the description of autopsy and biopsy findings in BEN patients by several other authors (cited in 8). We have already provided evidence in our previous publications (1,15) that the average incidence and severity of these sclerotic and atrophic changes in BEN significantly exceed those described as age-related in human kidneys (17,23,24) and a hypothesis has been raised by our group of an accelerated kidney ageing process in BEN (1,15).

Since its discovery, over five decades a number of hypotheses about the tentative etiopathogenesis of BEN have been raised, discussed, investigated, several rejected, but the real cause of the endemic disease still remains a great enigma. Long-lasting, low-dose expo-

Table 1. Incidence of various histomorphological changes in kidney tissue samples of 50 BEN patients and 50 age-matched control subjects

HISTOLOGICAL CHANGES - location and type	BEN (n=50) Positive cases No. (%)	Control (n=50) Positive cases No. (%)	χ^2 P value
TUBULO-INTERSTITIAL CHANGES			
Tubular atrophy	48 (96.0)	23 (46.0)	<0.0005
Interstitial sclerosis	49 (98.0)	20 (40.0)	<0.0005
Cell infiltration	19 (38.0)	5 (10.0)	<0.005
GLOMERULAR CHANGES			
Sclerosis global	40 (80.0)	18 (36.0)	<0.0005
segmental	5 (10.0)	0	
Hyalinosis	4 (8.0)	0	
GBM double outline	11 (22.0)	0	<0.005
Fetal-like glomeruli	4 (8.0)	0	
Hypercellularity	2 (4.0)	0	
VASCULAR CHANGES			
Hyalinosis	35 (70.0)	6 (12.0)	<0.0005
Sclerosis	26 (52.0)	4 (8.0)	<0.0005
Fibroelastosis	15 (30.0)	5 (10.0)	<0.005
Mucoid fibrosis	2 (4.0)	0	

Abbreviations: BEN - Balkan endemic nephropathy, GBM - glomerular basement membrane

sure of genetically predisposed family members in endemic rural settlements along the Danube and some of its tributaries to yet unidentified agent(s), both nephrotoxic and carcinogenic, seems to be the most logical and the most widely accepted frame for further investigation of a number of possible candidates. An accelerated ageing process caused by low-dose long-lasting exposure to environmental physical/chemical agent(s) could comprise both slowly progressive atrophy and sclerosis, particularly vascular, as well as carcinogenesis, and fits well into this frame. We know from experimental rats that there are factors that may significantly facilitate the ageing process, e.g. a protein or lipid overload diet (28, 29, 30). Similar discussion about the possibility of accelerated ageing has been raised with regard to human and experimental studies of lithium intoxication (31), and also with regard to mycotoxin ochratoxin A induced kidney lesions such a possibility should be considered (32). Furthermore, it might be of interest to note that the increased incidence and extent of sclerosing atrophy of nephron compartments, particularly tubulo-interstitial, compared to age-matched control groups have been obtained in studies of kidney involvement by nephrotoxic metals, e.g. lead, cadmium and lithium (31,33,34). All these inorganic and organic substances, currently of particular significance ochratoxin A, have been included on a long list of environmental nephrotoxic agents potentially causally related to BEN.

In considering the hypothesis of accelerated kidney ageing in the development of BEN, there are some important questions that remain to be answered. In patients older than 50 years of age, the distinction between abiotrophic involutional sclerosis and disease-related sclerosis in the kidney becomes less clear (23). The pathogenesis of these changes as an expression of kidney ageing is still incompletely understood and it still remains to be investigated whether simple ageing can ever cause the global renal failure which almost regularly occurs in BEN patients, usually between 40 and 60 years of age (35).

Recently, two substances among fungal and plant metabolites, ochratoxin A and aristolochic acid, which are suggested to be both nephrotoxins and genotoxic carcinogens, have deserved special interest as candidates for causal agents in BEN. Ochratoxin A causes preneoplastic lesions in the kidney of experimental rodents. Furthermore, ochratoxin A causes well known porcine nephropathy, a progressive kidney disease, suggested as an animal model of BEN (32). Nevertheless, no direct epidemiological evidence for a causal relationship between mycotoxin and BEN has yet been presented. Aristolochic acid can be isolated from the roots and seeds of the widespread weed, Aristolochia clematitis. A hypothesis of aristolochic acid as a possible etiologic agent in BEN has resurfaced due to recent reports of rapidly progressive tubulo-interstitial renal disease in a number of young women in Belgium who had been on a slimming regimen with pills including Chinese herbs and, by mistake, aristolochic acid (18). There are striking histomorphological similarities between Chinese herbs nephropathy and BEN, having in common a characteristic renal cortical histotopography of sclerosing parenchymal atrophy, particularly hypocellular interstitial fibrosis, and association with upper urinary tract atypical urothelial hyperplasia and transitional cell carcinoma (36).

While the most frequent and extensive histopathologic features seen in the kidney of early BEN patients are those of ageing, other microscopical findings, although less frequent, were observed in BEN patients only and never in the control age-matched group (Table 1). Scattered glomeruli showing an obvious segmental or global thickening of the capillary walls with a double-outline of the glomerular basement membrane were found in 11 (22%) out of 50 biopsies of early BEN patients. Corresponding electron microscopical focal segmental widening of the glomerular capillary wall subendothelial space, swelling of the endothelial cells, subendothelial neolamina densa and mesangial matrix widening, were found occasionally. By immunofluorescence microscopy, lumpy glomerular capillary wall IgM and C3 focal segmental or global deposits were demonstrated in 6 out of 50 BEN patients. In addition, mucoid intimal arterial hyperplasia was demonstrated focally in 2 BEN patients. All these changes represent a histopathology suggesting thrombotic microangiopathy of an unusually limited, focal distribution pattern. Thrombotic microangiopathy characterizes a group of diseases having in common endothelial cell injury in small blood vessels by various mechanisms, e.g. immune, infective or toxic. Multifocal vascular changes in BEN are fairly impressive and probably not only secondary to the much better known tubulo-interstitial histopathology. They have already been described in several autopsy studies in the past (3-5,7,14,37), but biopsy studies alone have confirmed that they occur even in early BEN, probably simultaneously with tubulo-interstitial renal changes and not consequentially (1,15). It is not therefore surprising that the terms pan-nephritis and nephronitis were introduced by some authors in order to characterize the histopathology of BEN (6).

It seems reasonable to assume that a hypothetical agent similar to a fungal metabolite and immunosuppressive drug cyclosporine, affecting more or less all nephron structures, with endothelial vascular cell being the main target, might be involved in the pathogenesis of BEN. This hypothesis was already raised in our previous publications (1,15) and almost simultaneously and independently by Sindjić (cited in 8). The cyclosporine-associated pathology comprises thrombotic microangiopathy (hemolytic-uremic syndrome), acute tubular nephrotoxicity and chronic nephrotoxicity, including hyalinizing microangiopathy with striped interstitial fibrosis and tubular atrophy (38). The histopathology of BEN shares similarities with chronic cyclosporine nephrotoxicity. Multifocal confluent interstitial fibrosis accompanied by tubular atrophy by an as yet unclear mechanism has been repeatedly described in BEN. Mi-

croangiopathy in chronic cyclosporine nephrotoxicity has been described as a characteristically external nodular arteriolohyalinosis but, according to our own experiences, it even more often shares similarity with predominantly internal, subendothelial or transmural arteriolohyalinosis, frequently pronounced in BEN patients as we have previously described (1,15) and which had also been pointed out even before by the others (cited in 8). No changes characterizing acute tubular cyclosporine toxicity or acute cyclosporine-related thrombotic microangiopathy, expressed clinically by acute hemolytic-uremic syndrome, were observed in our BEN patients, but changes which could be described as mild multifocal chronic thrombotic microangiopathy, clinically obviously inapparent, were found in our study to be not infrequent even in early BEN.

As early as the sixties, Nikulin and Rotter (37) suggested lesions of peritubular capillaries in BEN caused by a hypothetical toxic substance. Obliteration of peritubular capillaries and venous outflow tract disturbances were described by Dammin (5). Dojčinov et al (39) and Sindjić recently, as well as in the past (8), highlighted the significance of peritubular capillary changes in the pathogenesis of BEN. Systematic study performed by our group using electron microscopic and immunohistochemical techniques (1,15,40,41) has definitely confirmed the existence of a peritubular capillary pathology even in early BEN. Significant peritubular capillary basement membrane thickening and splitting seems not only to participate in the development of capillary sclerosis but also, by spreading of splitted capillary basement membrane layers as well as tubular basement membrane multiplication, participate in the development of interstitial sclerosis. Transplant glomerulopathy represents a peculiar form of thrombotic microangiopathy triggered by rejection, which was confirmed by our study to be associated with similar peritubular capillary involvement by the same mechanism (42). It seems reasonable to conclude that the observed multifocal peritubular capillary sclerosis associated with similar focal involvement of glomerular capillaries in BEN patients may represent a peculiar milder form of chronic thrombotic microangiopathy, caused by as yet unknown etiologic agent(s).

An immune etiopathogenesis of BEN has been suggested by several studies in the past by Romanian, Bulgarian and some Yugoslav authors, who based their opinion on BEN as a form of endemic immune complex-mediated glomerulonephritis (cited in 8). The hypothesis has never been founded on objective arguments and has to be rejected, although immune complex glomerulonephritis, such as glomerulonephritis IgA, may develop as coincidental in BEN patients, as demonstrated in our previous study (2).

The hypothesis of a viral etiology of BEN sounds attractive and was supported in the past by electron microscopic findings of virus-like particles in kidney biopsy samples of BEN patients (cited in 8). No scientifically convincing evidence has been provided by our studies to confirm this hypothesis. Molecular genetic techniques may represent a challenge in planning future research on BEN.

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