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Case Report

The Possibility of Scar Formation Due to Intrarenal Reflux in Analgesic Nephropathy

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Summary. Using an autopsy case of a 59-year-old man with analgesic nephropathy, papillary necrosis, and nephrolithiasis, it is shown that analgesic nephropathy may be complicated by damage resulting from intrarenal urine reflux. The morphologic alterations characteristic of intrarenal and/or pyelointerstitial reflux are caused by high intrapelvic pressure values during episodes of renal colic. Bacterially infected and possibly also sterile urine is then forced into the interstitium, directly within the papillary defect or indirectly via the tubular system after rupture of the tubule. The result is a severe interstitial process with inflammation, destruction, and scarring.

Key words: Analgesic nephropathy – Intrarenal reflux – Papillary necrosis – Nephrolithiasis

Introduction

In adults, damage to the renal parenchyma after intrarenal urine reflux has been reported in vesicoureteral reflux, urinary tract obstruction, and colic due to renal and/or ureteral calculi (McGovern and Marshall 1969; Estes and Brooks 1970; Servadio and Shachner 1970; McAninch and Campell 1973; Kincaid-Smith and Becker 1978). It has not yet been fully clarified whether the lesions are caused only by reflux of infected urine (Kincaid-Smith and Becker 1978; Heptinstall et al. 1979; Ransley and Risdon 1979) or whether they also develop with sterile reflux (Hutch and Smith 1969; Rolleston et al. 1974; Hodson 1979).

Reflux events occurring in association with analgesic nephropathy (AN) have not been reported in the literature. Papillary necrosis and nephrolithiasis are complications which usually appear in the advanced stages of AN; papillary necrosis has also been observed in the early stages (Gloor 1965, 1974; Burry 1967). They are detected during episodes of renal colic. Intrarenal reflux is possible in papillary necrosis with and without calculi formation, because intra-

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pelvic pressure is high during the colic. Histologic examination of several renal biopsy specimens from patients with AN revealed kidney damage such as found in reflux nephropathy. A similar autopsy case with clinical data is discussed below.[1]

Case report

First anamnesis The man, who died at the age of 59, had a history of at least 15 years of analgesic abuse, total phenacetin consumption amounting to several kilograms. Analgesic abuse was attributed to a painful injury inflicted during military service in World War II (gunshot fracture of the right shoulder). The drugs were ingested in uncontrolled amounts. The injury was officially declared a war disability (50% disability initially and then 60%).

Renal insufficiency was first diagnosed in 1975 (serum creatinine values, 2.5–3.0 mg%). Retention values increased gradually in the years following. In 1977, a recurrent duodenal ulcer necessitated a vagotomy and pyloroplasty; serum creatinine values at this time ranged from 3.0–4.0 mg%. In 1978, serum creatinine values at control examinations made every eight weeks between 2.2 and 4.4 mg%.

Last Anamnesis Fifteen days before death, the patient noted the passage of either a kidney stone or fragments of papilla; further episodes of renal colic could neither be confirmed nor eliminated on the basis of the case history. He also complained of vomiting and diarrhea. At hospital admission two days later, the patient was disoriented and had difficulty swallowing. Two days after admission, serum creatinine concentration was 7.2 mg%; the patient was then transferred to a dialysis unit. Intermittent dialysis was instituted three days later. After developing convulsions which could have been due to uremia, the patient was intubated and placed on a respirator. He developed acute bronchitis (examination of bronchial secretion showed klebsiella and pseudomonas) and pulmonary edema. The patient died of respiratory and cardiovascular insufficiency.

Laboratory Values for Final Period of Hospitalization. Serum creatinine concentration: maximal 8.3 mg%, approximately 6 mg% with dialysis; urea: maximal 279 mg%; Hb: 7.1 to 9.3 g%; blood pressure values: systolic, 100–170 mm Hg; diastolic, 80–100 mm Hg; uric acid: maximal 11.2 mg%; electrolyte levels were balanced via therapeutic measures.

Excerpts from the *pathoanatomic diagnosis* (autopsy report 178/79): Typical phenacetin kidneys with papillary necrosis and alterations, i.e., reflux pyelonephritis with retracted scars in the renal cortex (diagnosis based on post-mortem examination of paraffin-embedded material at our institute); heart (weight, 400 g) bilaterally hypertrophic with focal stenosis of coronary arteries; signs of chronic lung congestion; acute suppurative tracheobronchitis; disseminated bronchopneumonia.

Deeply retracted scar tissue above the right shoulder blade; abnormal flexibility of right shoulder joint. *Primary Disease.* Chronic fibrosing interstitial nephritis such as found with phenacetin abuse. *Cause of Death.* Uremia, terminal bronchopneumonia.

Detailed Histologic Examination of Renal Tissue (Fig. 1)

Chronic diffuse fibrosing interstitial nephritis with severe tubular atrophy and hyalinization of many glomeruli, particularly in the subcapsular zone; aseptic papillary necrosis, in situ and as papillary defect after papillae fragments were sloughed off; signs of final renal failure with dilated tubular lumina in undestroyed sections of the cortex; severe arteriosclerosis and arteriolosclerosis.

[1] The autopsy material and clinical data were supplied by Prof. Dr. H. Otto, director of the Institute of Pathology, Dortmund City Hospital, Dortmund/FRG

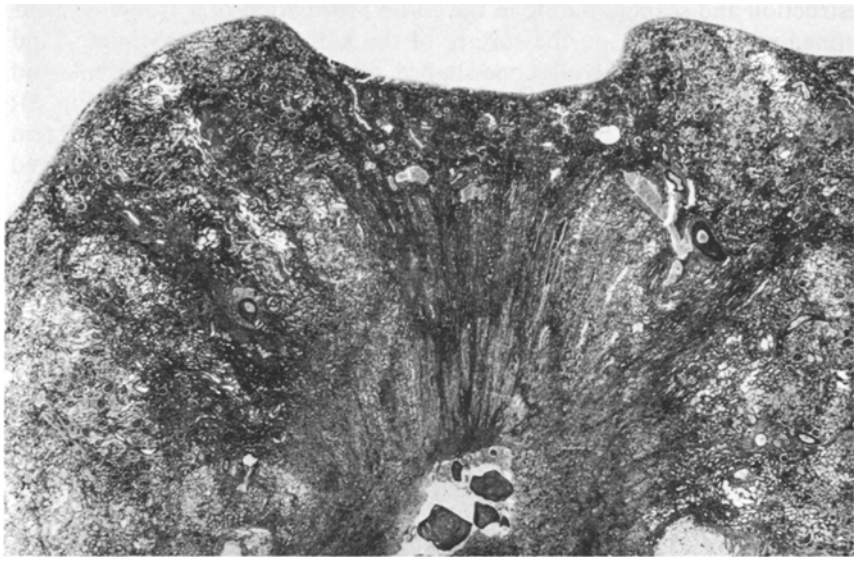

Fig. 1. Typical reflux scar in a case of analgesic nephropathy with partial papillary necrosis, renal calculi, and sharply defined scar tissue overlying papillary necrosis

Fig. 2. Partial papillary necrosis with scarring, nephrolithiasis, and suppurative pyelitis (detail from Fig. 1)

Destruction and scars radiating to the cortex; formation of a trough-shaped, well-defined retracted area on the surface of the kidney (due to shrinkage and substance loss in the underlying cone-shaped region between the papilla and the renal capsule around a partially necrotic, defective papilla, see Fig. 2); densely located glomeruli in various stages of hyalinization; tubular system extensively destroyed; high-grade atrophy in remaining tubules with thickened basement membrane; concentric thickening of arterial walls; narrowed lumina. Several small calculi surrounded by massive quantities of neutrophilic granulocytes and completely eroded urothelium were found in the renal pelvis.

Discussion

This case illustrates that intrarenal reflux and its sequalae may play a role in AN. A similar hypothesis has not been reported in the literature.

In addition to vesicoureteral reflux and urinary tract obstruction of different etiologies, intrarenal reflux and subsequent scarring can develop in connection with renal colic (McAninch and Campell 1973). Morphologically, the concept of reflux nephropathy should include all types of damage to the renal parenchyma which can be attributed to intrarenal reflux of urine, regardless of whether the cause is a vesicoureteral reflux or a reflux in the upper urinary tract. Renal colic may be caused by the passage of papillae fragments after partial papillary necrosis or of calculi from the renal pelvis into the ureter. Intrapelvic pressure increases during the colic. In the case described here, the result was pyelotubular and/or pyelointerstitial reflux in the region of the papillary destruction. Although there was no positive anamnesis of bacterial urinary tract infection, the abundance of neutrophilic granulocytes in the renal pelvis tended to indicate that infected urine reflux may have been present at least in the final phase of the patient's life.

This finding however does not eliminate the possibility that a similar histologic picture could also have been produced by a sterile reflux with high pressure values. Renal scars after confirmed sterile reflux have been reported by several authors (Hutch and Smith 1969; Rolleston et al. 1974; Hodson 1979). The exact pathogenetic mechanism of such damage to the renal parenchyma is still unknown.

Renal cortex scars are not rare findings in AN. The development of these scars has been explained by secondary scarring of the associated tubular apparatus via papillary and/or medullary fibrosis or necrosis (Kincaid-Smith 1965; Burry 1967; Gault et al. 1971; Gloor 1974). Other authors have emphasized "the relative absence of coarse scars in the cortex in AN" (Lee et al. 1974). The extent and/or depth of the cortical scars does not appear to depend necessarily on the extent of the papillary necrosis. Only slight scarred retractions of the kidney surface or none at all (Fig. 3) therefore are observed in other cases with comparable papillary necroses. The picture we described, however, shows variations which, even though not pathognomic, are still typical for the condition after pyelointerstitial reflux. In the case presented here, partial papillary necrosis

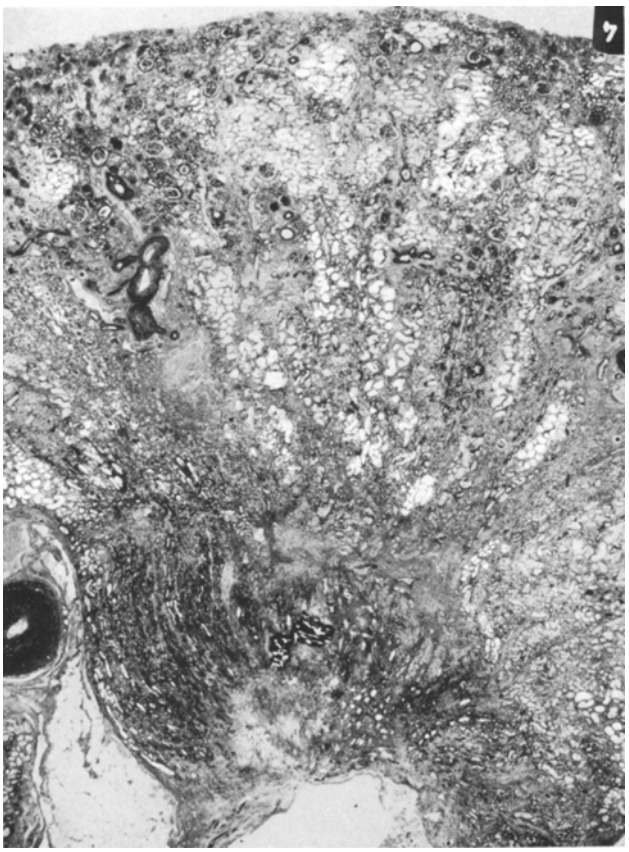

Fig. 3. Advanced stage of analgesic nephropathy (serum creatinine > 6 mg%) with interstitial fibrosis of cortex and medulla, partial papillary necrosis and circumscribed calcification, but without evident scarred retractions (63-year-old man)

with immediately adjacent, striped scarring directed toward the cortex was found only in one central section of the corresponding kidney segment. Compared with the extent of the partial papillary necrosis, this deeply retracted scar was impressive. The scar tissue differed histologically from that of a juvenile reflux kidney not only because of the absence of a characteristic histologic picture (Laberke. Morphology of reflux nephropathy, in preparation), but also because of the scar formation after analgesic-induced parenchymal damage.

It is difficult to evaluate the significance of intrarenal reflux as a "complication" of an existing complication of AN, namely papillary necrosis and/or nephrolithiasis. We rarely saw this type of alteration in our histologic examination of more than 130 cases of AN (120 biopsy specimens, the rest nephrectomy and postmortem specimens). The damage may well-depend on other factors, such as diuresis at the time, degree of intrapelvic pressure, duration of renal colic and/or frequency of recurrence, or actual microorganism causing the urinary tract infection during the colic. In addition to the damage associated

with AN, functional impairment can also be assumed if reflux damage is more extensive.

Since the conditions for intrarenal reflux phenomena described here may already be present in the early stages of AN, the further deterioration of renal function can be important for the prognosis.

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