CHRONIC UNILATERAL PYELONEPHRITIS AND MALIGNANT HYPERTENSION

CASE WITH SPECIAL REFERENCE TO JUXTAGLOMERULAR CELLS AND INTERTUBULAR CELL ISLETS

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Frequent association of hypertension in cases of chronic unilateral pyelonephritis is well known [26], but the underlying mechanisms are still uncertain. After Goldblatt established that renal hypertension is caused by liberation of renin, various structures in the kidney have been suspected to be the site of renin formation. Among them are the eqitheloid cells in the arteriolar wall and the intertubular cell islets. The epitheloid cell was first described in the kidney of mice by Ruyter [25] in 1925, and two years later in human kidney by Oberling [21]. Various names, such as Goormaghtigh's cell and juxtaglomerular cell, have been attached to this cell. The intertubular cell islet was described by Becher [3] and is now known by his name. According to Feyrter [9], it is essentially identical with the irregular outgrowth of the renal tubule which Peter [23] had earlier described as *"endophytische Sprossung"*. Reports on these structures, especially on the latter, are relatively scarce. This communication reports a case of chronic unilateral pyelonephritis which presented an interesting feature of the epitheloid cells being demonstrated in the affected kidney and the intertubular cell islets in the other kidney.

A CASE REPORT

The patient was a 26-year-old male who was first noted to have hypertension and suspected pulmonary tuberculosis in April, 1954. The pulmonary tuberculosis was improved by the subsequent chemotherapy. He continued to have sustained high blood pressure of about 220 mm Hg., systolic, frequent headaches and insomnia. He then noticed thirst and increased urine volume, and these symptoms persisted towards his death. In February, 1955, he began losing visual acuity first of the left and then of the right eye, and was subsequently diagnosed as having hypertensive retinopathy. He was admitted to the Yamaguchi Medical School Hospital on Apr. 16, 1955, because of high fever with shaking chills. Physical examination on ad-

mission revealed an enlarged heart and high blood pressure of 210/105. The hypertension was entirely unresponsive to medical treatment, and administration of a methonium compound even resulted in a slight elevation of the pressure. He had recurrent attacks of nocturnal dyspnea. A partial resection of the left adrenal was performed on Dec. 17, 1955, without therapeutic effect and he expired on Jan. 21, 1956.

Laboratory test: Urinalysis revealed proteinuria of 70 mg/100 ml, sediment containing a few leucocytes, red blood cells and epithelia per high power field and specific gravity ranging 1.007–1.010. No culture was made. Blood chemistry was unremarkable except for mild hypopotassemia and NPN which was at the upper limit of the normal range. The Thorn's test and 17-ketosteroid excretion were normal before the operation.

AUTOPSY FINDINGS

Autopsy was performed 4 hours after death. The body was that of an emaciated male with moderate edema of the lower extremities and ascites of about 1 liter. There were furuncles around the nose.

Kidney: The right kidney was small, weighing 100 gm. The decapsulation was difficult and a depressed scar was seen on the surface. On section, 8 renal pyramids were counted and the thickness of the cortex measured 2 mm. Several yellow streaks of suppurative lesions were seen in the medulla. Renal pelvis was not dilated and the mucous surface was grossly normal. In contrast, the left kidney was very large, weighing about 300 gm. The renal capsule was stripped with difficulty, exposing the surface punctuated with numerous abscesses of pin-head size. The same abscesses were scattered also on the cut surface. The cortex was 8 mm in thickness and there were 12 renal pyramids. A distinct difference in color was noted between the two kidney: the right kidney being dark red and the left, pale. There was no abnormality in the lower urinary tract.

Heart: Hypertrophied and dilated, weighing 430 gm. The thickness of muscle wall was 26 mm at the middle of the left ventricle.

Lung: Lung tissue was generally felt harder than normal. The cut surface was brownish red. There was one large suppurative lesion with a cavity of about 12 mm in diameter in the left upper lobe. Multiple foci of suppuration were scattered in both lungs. No caseous lesion was found.

Other organs: The liver and the spleen were enlarged. A number of submucous hemorrhages were seen in the stomach. A small area of the duodenal wall was thickened by submucosal hemorrhage. No gross abnormalities in the other organs.

MICROSCOPIC FINDINGS

Kidney: The kidney was cut *in toto* in one section and all the field was care-

fully examined. Each kidney revealed abnormalities of entirely different characteristics.

In the right kidney, atrophic areas were seen in patchy distribution which might account for its small size. These areas were marked with groups of atrophic tubules containing colloid casts in their narrow lumina. The tubular epithelia were flattened. The lumina were reduced in caliber and even closed in some. The interstitial tissue in these areas was infiltrated with lymphocytes and a few plasma cells (Fig. 1).

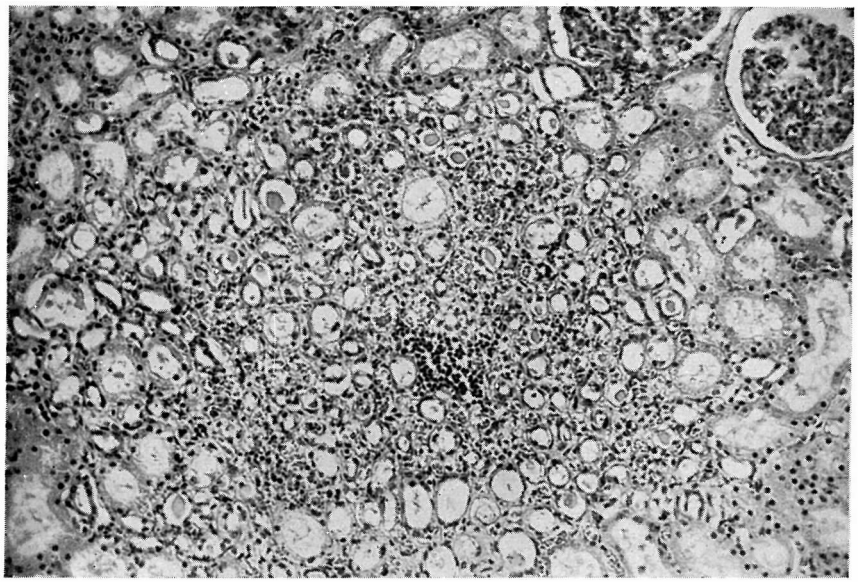

Fig. 1 Atrophic tubules in the right kidney.

The interstitial tissue is infiltrated with lymphocytes and a few plasma cells. Some of the tubules contain colloid casts. Rich network of dilated capillaries is visible between the atrophic tubules. (Hematoxylin and eosin: × 150)

Careful examination made of a number of sections disclosed that these atrophic tubules roughly correspond to the distal convolutions and the proximal segments of the collecting tubules. There was a rich network of dilated capillaries in the atrophic areas and immediately under the renal capsule. Cellular infiltration was restricted in and around the atrophic areas. Connective tissue proliferation was not observed except in the scar in the subcapsular zone. The glomeruli were generally atrophic, a few showing capsular crescent formation; the majority of the crescents had undergone fibrosis.

The most characteristic change in the right kidney was that of the preglomerular arterioles and of the interlobular arteries. Their wall, particularly the media, was hypertrophied. The muscular element of the media was largely replaced by round

or polygonal cells. These cells were strikingly large and had a round or indented nucleus. The cytoplasm was clear. Goldner's trichrome stain did not reveal cytoplasmic granules, probably because of formaline fixation (Fig. 2). Other characteristics of these cells coincided with those of the so-called "epitheloid cells" of renal arterioles. These vascular changes were more frequently encountered in the periphery of the scar and in both poles of the kidney. The intercalated cells of the collecting tubules were increased in number.

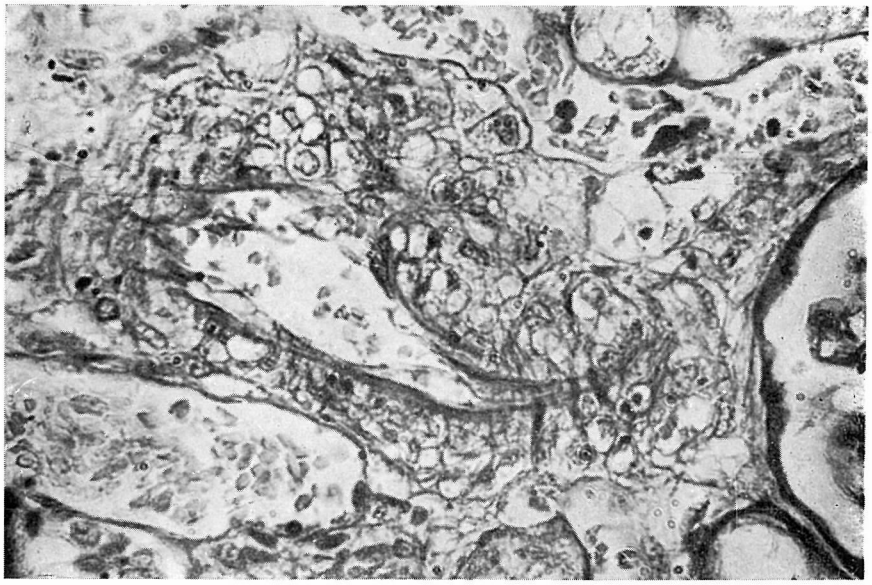

Fig. 2 Epitheloid cells in a preglomerular arteriole of the right kidney.

The cells of the arteriolar media are transformed to large, polygonal cells with clear cytoplasm. Cytoplasmic granules are not evident. (Formaline fixation, PAS stain: × 580)

In the left kidney, there were distributed in the parenchyma numerous suppurative foci of recent occurrence. In other places infiltration of neutrophilic leucocytes predominated around the tubules, while the tubular epithelia were less frequently involved. Colonies of Gram-positive cocci were found in many of the glomerular tufts. The tubules were not dilated, but their basement membrane was greatly thickened.

The most peculiar feature in the left kidney was the presence of large oval or polygonal cells in the intertubular spaces (Fig. 3). These cells had a large nucleus and a typical clear cytoplasm which sometimes appeared to be vacuolated. The cytoplasmic granules were not observed. They were arranged in rows in the intertubular spaces and were clearly separated, in most part, from the tubular epithelium

by a basement membrane. In a few places, however, continuity of the basement membrane of the proximal convoluted tubules was lost and these cells were in direct contact with tubular epithelium, suggesting their transformation to the intertubular cell islets. Lateral outgrowth of tubular wall, or the so-called "*endophytische Sprossung*", was not found anywhere. These cells were separated from each other by a thin layer of PAS-positive substance. In some places they were even enclosed

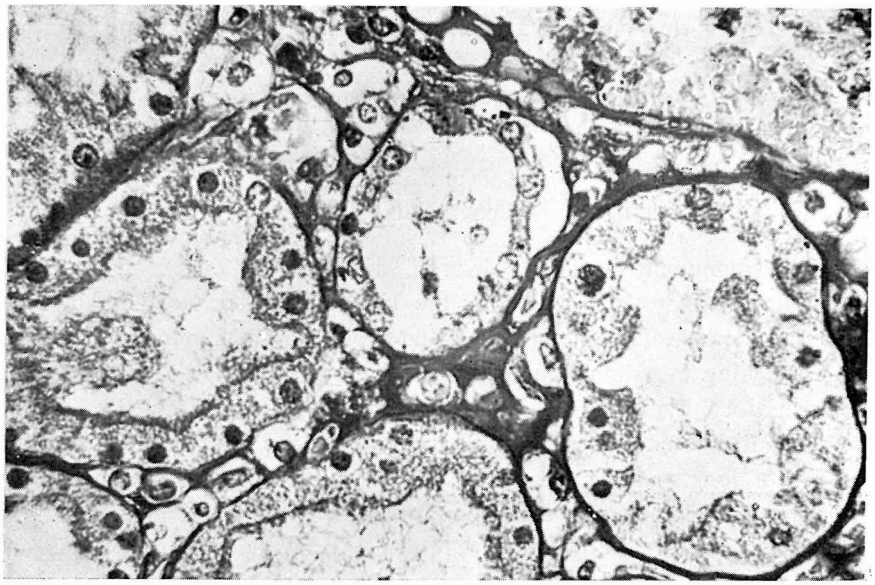

Fig. 3 Intertubular cell islets in the left kidney.

The basement membrane of a tubule has partly disappeared and the tubular epithelium is in direct contact with Becher's cells, suggesting a transformation of the former to the latter. (Formaline fixation, PAS stain: × 580)

separately in amorphous mass of PAS-positive substance. Although these cells existed mostly between the tubules, they were found also around the arterioles, where the transition to these cells was gradual with an indistinct boundary. The presence of these cells was restricted within a relatively small area near the lower pole of the left kidney. Afferent vessels of the glomeruli were generally unaffected, but intimal elastosis of arteries was much more marked in the left kidney than in the right.

Heart: Muscle fibers were hypertrophied. There was a scar with a small abscess in a papillary muscle.

Lung: Alveolar walls were congested and markedly thickened by heavy infiltration of plasma cells and neutrophils; fibrosis was not marked. The lining epithelium was cuboid or columnar, showing an acinus-like appearance. The arterioles in the pulmonary tissue showed marked medial hyperplasia. In the alveolar space there

were sideroferous macrophages and erythrocytes, and some of the alveoli were filled with neutrophilic leucocytes and fibrinous material. Abscesses were formed in many areas. These changes were found in patchy distribution. Bronchioles in the inflammatory areas were filled with neutrophils and desquamated epithelia.

Liver: Fibrosis and hemorrhage were noted around the central veins. Sinusoids were generally dilated, and hepatic cells showed minimal fatty degeneration.

Spleen: Marked congestion and thickening of the wall of the central arterioles.

Stomach: Mucous membrane showed hypertrophy with catarrh.

Thyroid gland: Infitration of neutrophils and abscess formation in the interstitial tissue.

Lymph nodes: Acute lymphadenitis with occasional suppuration in various parts of the body.

DISCUSSION

The right kidney may be called "dwarfed kidney" (Mathé [18]). The weight was about 30 gm less than the average for the Japanese of the age [1]. Although the definition of hypoplastic kidney is somewhat arbitrary, and some authors [2,4] define it as one weighing less than 60 gm, this right kidney is significantly small as evidenced by compensatory hypertrophy of the other kidney. It is presumed, from the marked weight difference between the two kidneys, that the condition in the right kidney was of long standing. A question is to be asked whether or not the small size of the right kidney was of a congenital nature. Some of the histologic findings of the kidney support the diagnosis of chronic pyelonephritis conforming to the criteria of Weiss and Parker [28], which include infiltration of lymphocytes and plasma cells in the interstitial tissue, presence of the so-called colloid casts in the tubules lined by atrophic epithelia, and pericapsular fibrosis. Yet, some structural abnormalities to be discussed later suggest a congenital origin. The problem is how to differentiate microscopic characteristics of embryologic maldevelopment from those secondary to chronic atrophic pyelonephritis. Weiss and Parker [28] preferred chronic pyelonephritis to congenital hypoplasia as the cause for small kidneys, regarding the process in those kidneys as representing infection which has begun in childhood and has resulted in subsequent scarring and aberrant growth. Marshall [17], in a series of kidneys of infants and children, described following structures as remnants of fetal structure: 1) primitive tubules, 2) rudimentary glomeruli, 3) abundant cellular tissue separating the tubules, 4) capillary network, and 5) delta-like medullary pyramids. Zollinger [30] offered criteria which include paucity of renal pyramids.

In the present case, the right kidney differs macroscopically from the normal in that it has fewer pyramids. A cavernous capillary plexus in and around the area of atrophic tubules also suggests a congenital maldevelopment. It might be on this basis that the right kidney was infected. The capillary network could have facilitated

infection through a mechanism similar to that postulated by De Navasquez [7]. Absence of diffuse fibrous contraction may mean that the infection had occurred in early infancy. Porter and Giles [24] reported that chronic pyelonephritis occurring in early infancy differs from that of the adult in two respects: 1) macroscopically, there is seldom asymmetrical contraction or coarse, shallow scarring, and 2) microscopically, crescents of varying numbers are prominent. Similar observations were made by Claireaux and Pearson [6].

The mechanism for the hypertension in this case can only be speculative. The changes of the arterioles in the right kidney may be called "hyperplastic arteriolosclerosis" (Weiss and Parker [28]). The unique feature of this case was the abundance of large polygonal cells in the arteriolar media which are generally called "epitheloid cells" or "juxtaglomerular cells". It is to be noted that the epitheloid cells were found only in the right kidney which had chronic pyelonephritis and should therefore be responsible for hypertension. Since Oberling [21] first mentioned the possibility that the epitheloid cells play a role in the development of hypertension, many reports have appeared in which hyperplasia and hypertrophy of the epitheloid cells were observed in the inflammatory kidneys (hypertensive pyelonephritis, [15, 16, 27] acute, subacute or chronic glomerulonephritis [8, 13, 15, 19] and in other types of hypertensive diseases [8, 10, 11, 13, 15, 16]). Although many authors including Goormaghtigh [12] and Kaufmann [16] suggested that the epitheloid cells produce vasoactive substance, Oberling [22] in 1944 objected to their hypothesis on the reasons that there is no parallelism whatsoever between the degree of hypertension and development of these cells and that in severest cases of hypertension they are generally degenerated. Bohle [5] recently concluded, after studying 145 human kidneys, that these cells were encountered rather less frequently in the kidneys of hypertensive patients than in normotensive controls. He inferred that the epitheloid cells increased as a result of a response to lowered intrarenal blood pressure. This might be true of this case, because intimal elastosis of arteries which is a morphological expression of hypertension was slightest in the right kidney while it was very marked in the left. The factor that lowered the blood pressure in the right kidney may have led to the reduction of renal blood flow and consequent development of renal hypertension. This, admittedly, is a mere supposition.

The peculiar cell group observed in the intertubular space must be identical with what is called "intertubular cell islet" or "Becher's cell". When Becher [3] first described it, he pointed out its structural relationship with the arteriole. In this material, however, it was found more frequently in association with the tubule like Neuman's observation [20], and was distinct from Goormaghtigh's cell. Transition of the tubular epithelium to the intertubular cell islet was suspected, but in contrast to Feyrter's view, the tubular epithelium appeared to have dissolved the basement membrane and proliferated in the intertubular space. As to the functional significance of the intertubular cell islets, Feyrter [9] postulated that they produce a sub-

stance that acts as a vasodilator. Zollinger [29] thought to the contrary that they produce renin. It is interesting to note that Becher's cell was not found in the right kidney of this case. This may be simply due to a greater increase of the Becher's cells in the left kidney than in the right, rendering these cells recognizable as such only in the former. Should the Becher's cells be the ones that produce renin, they must be found in increased numbers in the kidney which is responsible for hypertension. Therefore, our observation contradicts Zollinger's view, so long as the chronic pyelonephritic kidney was causing hypertension. Further inquiry into the problem is not feasible because of the limited number of the case studied. It must be stressed, however, that studies of unilateral renal diseases with hypertension are extremely valuable in understanding whether these two types of cells play a causative role or a compensatory role in renal hypertension.

SUMMARY

A case of unilateral atrophic pyelonephritis with compensatory hypertrophy of the contralateral kidney was described with a special reference to juxtaglomerular cells and intertubular cell islets. The chronic infection in the right kidney probably originated in early infancy on the basis of congenital structural abnormalities.

In this kidney, the epitheloid cells were found to be increased in the preglomerular arterioles and the interlobular arteries. Such increase may be a morphological expression of a reduced intrarenal blood pressure. The intertubular cell islets, on the other hand, were observed only in the left kidney. Their role seems to be a compensatory one, even if they were related to hypertension in some unknown manner.

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