Case Reports

A Case of Alport's Syndrome with Retinitis Pigmentosa sine Pigmento

Ryosei Ueda, MD, Takashi Kaku, MD, Shinichiro Ohkawa, MD, Satoru Matsushita, MD, and Mototaka Murakami, MD

A female patient found to be suffering from Alport's syndrome is reported. The patient was first seen to have proteinuria at the age of 25. Thereafter diagnoses of retinitis pigmentosa sine pigmento and nerve deafness were made. She died of uremia at the age of 64. Chronic nephritis, nerve deafness, and myopia were found in her family. The histologic pattern of the kidneys was consistent with chronic glomerulonephritis. Electron microscopy showed diffuse irregular thickening and splitting of the lamina densa in the glomerular basement membrane. The association of Alport's syndrome with retinitis pigmentosa sine pigmento has not here-to-fore been reported.

Key Words: Alport's syndrome, Retinitis pigmentosa sine pigmento, Nerve deafness, Chronic glomerulonephritis, Diffuse irregular thickening of the glomerular basement membrane, Splitting of the lamina densa

Hereditary nephritis was first reported by Dickinson in 1875, and Alport described the association of hereditary nephritis with nerve deafness for the first time. However, hereditary nephritis attracted little attention until 1951 when a large kindred afflicted with chronic renal disease and nerve deafness was described. Sohar reported the association of hereditary nephritis with ocular abnormalities as well as deafness, and Meier and Hess described a family in which hereditary nephritis and a retinitis pigmentosa coexisted. In this paper we have reported a case of Alport's syndrome associated with retinitis pigmentosa sine pigmento for the first time.

CASE REPORT

A sixty-two year old woman was admitted to Tokyo Metropolitan Geriatric Hospital because of constriction of the visual field, night-blindness and general malaise. Since the age of 25 she had been known to have proteinuria. Hypertension was found at the age of 46 and diagnoses of chronic nephritis and gout were made when she was 49 years old. She noticed night-blindness at the age of 54. When she was 58 years old, a constriction of the visual field with central scotoma was bilaterally noticed and the visual acuity was 0.2 in each eye. Laboratory studies revealed blood urea nitrogen 77mg/dl; creatinine 3.5mg/dl; uric acid 10.7mg/dl; sodium 144mEq/L; potassium 4.6mEq/L; and chloride 112mEq/L.

On admission the patient had clear consciousness, pale and dry skin and uremic breath. The height was 150cm, and the weight 39kg. The blood pressure was 150/88mmHg and the pulse rate 84 regular.

From Department of Internal Medicine, Tokyo Metropolitan Geriatric Hospital (Yoiku-in), Tokyo
Received publication July 11, 1977.
Reprint request to: Ryosei Ueda, MD, The Second Department of Internal Medicine, School of Medicine, Kanazawa University, Takaramachi 13-1, Kanazawa, Ishikawa prefecture, 920, Japan

beats per minute. Apical impulse of the heart was in the fifth intercostal space, 3cm to the left of the midclavicular line. An ejection murmur of Levine grade 2 was heard at the apex. The visual acuity was 0.15 (0.15X+1.0) D bilaterally. The peripheral visual field was constricted approximately 50 degrees in each direction. A ring scotoma was detected in each eye, measuring approximately 40 and 10 degrees respectively in the outer and inner margins. A threshold of dark adaptation was about 50 times higher than normal. Ophthalmoscopic examination revealed pallor of the optic discs and attenuation of the central retinal vessels. The fundi were tessellated, suggesting atrophy of the retina. The so-called bone-corpuscle like pigmentation was not visible. An audiogram revealed nerve deafness under 40db. over 2,000Hz. The remainder of the physical examination was within normal limits.

Laboratory studies showed blood urea nitrogen 83.5mg/dl; creatinine 4.8mg/dl; uric acid 9.8mg/dl; sodium 139mEq/L; potassium 4.9mEq/L; chloride 97mEq/L; arterial blood pH 7.40; hemoglobin 10.5gm/dl; and hematocrit 33.7 per cent. Aminoaciduria was not present. A twenty-four hour urine protein was 0.8 to 1.2g. A phenolsulfophthalein excretion was 5 per cent in 15 minutes and 20 per cent at 2 hours. Fishberg's concentration test revealed a specific gravity of 1.014. The creatinine clearance was 23.5ml per minute. An electrocardiogram demonstrated left ventricular hypertrophy. A Wassermann reaction was positive. Urine cultures were negative. Prothrombin time, fibrinogen, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase, and alkaline phosphatase were within normal limits.

She was discharged on a low sodium and protein diet.

Twenty-two months later, she suddenly lost consciousness and was readmitted.

On physical examination she was alert. There was edema on the face and both lower legs. The blood pressure was 158/60 mmHg and the pulse rate 100 regular beats per minute. The respiration was normal but a uremic breath was noticed. An ejection murmur of Levine grade 3 was heard at the apex, and flapping tremors of both hands were noticed.

Laboratory studies at the time of admission were as follows: blood urea nitrogen 170.0mg/dl; creatinine 13.0mg/dl; uric acid 10.9mg/dl; sodium 137mEq/L; potassium 7.0mEq/L; chloride 104mEq/L; calcium 2.4mEq/L; inorganic phosphorus 11.4mEq/L; arterial blood pH 7.26; hemoglobin 8.2gm/dl; and hematocrit 24.2 per cent. An electrocardiogram revealed an incomplete right bundle branch block, prolonged QT interval and left ventricular hypertrophy. An endogenous creatinine clearance was 1.7 L per day. The urine sediments showed 5 to 10 red cells and a few of white cells per high power field and occasional hyaline casts in the sediment. Aminoaciduria was not present. A twenty-four hour urine protein was 0.8 to 1.2g. A phenolsulfophthalein excretion was 5 per cent in 15 minutes and 20 per cent at 2 hours. Fishberg's concentration test revealed a specific gravity of 1,014. The creatinine clearance was 23.5ml per minute. An electrocardiogram demonstrated left ventricular hypertrophy. A Wassermann reaction was positive. Urine cultures were negative. Prothrombin time, fibrinogen, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase, and alkaline phosphatase were within normal limits.

She was discharged on a low sodium and protein diet.

Twenty-two months later, she suddenly lost consciousness and was readmitted.

On physical examination she was alert. There was edema on the face and both lower legs. The blood pressure was 158/60 mmHg and the pulse rate 100 regular beats per minute. The respiration was normal but a uremic breath was noticed. An ejection murmur of Levine grade 3 was heard at the apex, and flapping tremors of both hands were noticed.

Laboratory studies at the time of admission were as follows: blood urea nitrogen 170.0mg/dl; creatinine 13.0mg/dl; uric acid 10.9mg/dl; sodium 137mEq/L; potassium 7.0mEq/L; chloride 104mEq/L; calcium 2.4mEq/L; inorganic phosphorus 11.4mEq/L; arterial blood pH 7.26; hemoglobin 8.2gm/dl; and hematocrit 24.2 per cent. An electrocardiogram revealed an incomplete right bundle branch block, prolonged QT interval and left ventricular hypertrophy. An endogenous creatinine clearance was 1.7 L per day. The urine sediments showed 5 to 10 red cells and a few of white cells per high power field. A twenty-four hour specimen of urine contained 2.0 to 4.0gm of protein. Her general condition improved temporarily with disappearance of tremors. However, her renal function deteriorated progressively and she died on the 103rd hospital day at the age of 64.

PATHOLOGICAL FINDINGS

Fig. 1. Gross appearance of the kidneys show small and contracted kidneys with marked decrease in cortical thickness and obliterated corticomedullary junctions on cut section.
The major findings at autopsy were compatible with the end-stage of renal disease and consequent uremia. The kidneys were remarkably small and contracted, weighing only 30 to 40gm. The surfaces were finely granular. The cortices were markedly thin, corticomedullary junctions were obliterated and inflammatory changes were seen in the interstitium. Marked sclerotic changes were present in the intrarenal vessels (Fig. 1). Microscopically the sparse glomeruli showed various stages of hyalinization with some synechiae. In the glomerular tufts, hypertrophy of the basement membrane and proliferation of endothelial as well as mesangial cells were noted. The basement membrane of the Bowman's capsules was fibrously thickened.
The tubules showed varying degrees of degeneration and the tubular basement membrane was hypertrophied. There was a focal and diffuse infiltration of lymphocytes and plasma cells in interstitial spaces (Fig. 2). Foam cells were found in the corticomedullary junctions and distributed radially into the medulla (Fig. 3). The intimae of the intrarenal arterioles were so markedly thickened that the lumina were narrowed. On electron microscopy, the characteristic finding in the glomerular basement membrane was diffuse irregular thickening and splitting of the lamina densa (Fig. 4). The epithelial cells were swollen and their foot processes were partially fused. The capillary lumina were often narrowed by endothelial cells, edema and proliferation. The mesangium was widened, showing cell proliferation and an increase in mesangial matrix. The tubular as well as Bowman's capsular basement membranes were also irregularly thickened. The epithelial cells in the tubules were atrophic or swollen. Some tubules contained casts.

Findings in other than the kidneys were as follows: hypertrophy and dilatation of the heart (470g), cerebral edema with a moderate degree of cerebral arteriosclerosis (1,110g), slight degree of bronchitis and pulmonary emphysema (170gm. on the left, 210g. on the right), congestive liver (1,270g), congestive spleen (60g), parathyroidal hyperplasia of a slight degree, mixed bone marrow of the femur and red marrow of the vertebrae.

Chromosomal studies showed hetero polyploidism, however, neither chromosomal breakage nor translocation were noted.

PEDIGREE

The pedigree is shown in Fig. 5. The patient had four siblings, and one of them had three children. The results of examination were described in Fig. 5. Characteristically noted was as follows: the patient had chronic nephritis, nerve deafness and retinitis pigmentosa sine pigmento. Her sister showed hematuria, proteinuria of about 7.5g per day and nerve deafness. The patient's niece showed hematuria and nerve deafness and two of her nephews also showed hematuria. Myopia was found in all of them. The husband of the patient's sister was found to be normal.

DISCUSSION

The patient had chronic nephritis and bilateral nerve deafness, as well as retinitis pigmentosa sine pigmento. The microscopic pattern of the kidney was characteristic of chronic glomerulonephritis. Electron microscopically, the glomerular, tubular, and Bowman's capsular basement membranes were irregularly thickened. Splitting of the lamina densa was noted, but electron dense particles were not seen. She had no previous history of poisoning by any drug such as chloroquine. In her family, renal disease was consistently found. Nerve deafness was proven in her sister and niece. Myopia was found in all of them. These findings were strongly suggestive of Alport's syndrome, whether or not the particles were seen in the basement membrane.

In this syndrome the most common urinary abnormalities are hematuria and
A Case of Alport's Syndrome with Retinitis Pigmentosa sine Pigmento

proteinuria\textsuperscript{6,7). Pyuria, aminoaciduria, pro-

linuria, cylinduria and nephrotic syndrome are rarely noted\textsuperscript{9). Urinary findings are

known to vary with the stage of the disease even in the same person and among the

same family. Hematuria of various grades was proven in this family.

Uremia, of which the patient died, is the most common cause of death. As a

rule, the final stage appears at the second to third decade of life in males, and the

fifth to sixth decade of life in females. However, it is unknown why females live

longer than males.

The histological pattern of the kidney is consistent with chronic glomerulonephri-
tis. The interstitial foam cells are seen in some instances, which are thought not to be

derived from general abnormal lipid metabolism but to be derived from either
degenerated tubular epithelial cells or lipid-laden macrophages\textsuperscript{8,9). These cells,

however, are not a pathognomonic feature of this syndrome. In some occasions, foam
cells are demonstrated in nephrotic syndrome, glomerulonephritis, pyelonephritis,
de Toni-Fanconi syndrome with cystinosis, Wegener's granulomatosis, and renal

abscess\textsuperscript{10}.

Thickening of the glomerular, tubular and Bowman's capsular basement membranes

was reported as a pathohistological alteration found during the course of renal
deterioration in Alport's syndrome\textsuperscript{6,11). It has been demonstrated electron microsco-

pically that this thickening is due to a characteristic splitting of the lamina
densa\textsuperscript{11-14). In addition to the thickening of the basement membrane, an accumu-

lation of electron dense particles between the split layers attracted the attention of

some authors\textsuperscript{11-13). Hinglais et al\textsuperscript{12) described that the lamina densa was distorted

and transformed into a heterogenous network of strands enclosing clear electron-

lucent areas. These areas contained small, round granulations approximately 500Å in
diameter and such an ultrastructural change of the glomerular basement membrane

constitutes both specific and early morpho-

logic evidence. Similar granules or particles have been reported by Kinoshita

et al\textsuperscript{11} and Churg et al\textsuperscript{10), but they did not report the frequency that the material

appeared. Spear et al\textsuperscript{14) reported that the most impressive lesions, present in all pa-

tients, were thickening of the basement membrane and splitting and splintering of

the lamina densa, in a focal and local distribution and dense deposits were not

seen. In our case diffuse irregular thickening of the basement membrane and split-

ting of the lamina densa were demonstrated, but electron dense particles were not

noted. At present, we assume that these findings are strongly suggestive of

Alport's syndrome irrespective of the pre-

sence of the particles.

Hearing defects, which are related to progressive nerve deafness equally affect both ears. Although described in association with nephritis, it is not always in this syndrome\textsuperscript{6,7,15). In general, a loss of hearing is observed only with audiometry in females and our patient was unaware of it. Histologically nonspecific atrophy of the nerve cells of the spiral ganglion is reported\textsuperscript{16}.

Visual disturbances are rarely present. Lens defects are most frequently found and retinal abnormalities are uncommon among these\textsuperscript{5,8,17). Congenital cataracts, congenital nystagmus, myopia, spherophakia, anterior lenticonus, and retinitis pigmentosa have been reported\textsuperscript{5,8,17). However, retinitis pigmentosa sine pigmento, in which night-blindness and progressive constriction of the visual field are characteristic symptoms, has not been reported until now. Severe degrees of myopia were reported to be frequently associated with it. As a rule, night-blindness first appears at 6 to 12 years of age and loss of vision develops late in life. However, our patient first noticed night-blindness in her mid-fifties and never developed complete loss of vision. This disease is inherited as either an autosomal dominant or recessive trait in pedigrees.
which suffer from retinitis pigmentosa. However, a sporadicity cannot be denied in our case, since it is known that sporadic cases appear in quite intact pedigrees\(^1\). Consanguinity is frequently noted, but it was not demonstrated in our patient's pedigree.

It is generally accepted that Alport's syndrome is inherited as an autosomal dominant\(^2\). In a few of the previously reported kindreds, however, a disproportionately large number of affected female members were observed, and this made it necessary to invoke additional explanations for the mode of inheritance, such as preferential segregation\(^3\) or partial sex linkages\(^4\). Hearing defects appear to be a sex-linked recessive in inheritance, but it is impossible to decide whether it is caused by the same gene that produces the kidney disease, or by another gene on the X-chromosome\(^5\).

Although the pathogenesis of Alport's syndrome is not made clear at present, hypotheses are proposed, such as inborn error of metabolism\(^6,9,21\), metabolic defects of collagen\(^6\), slow virus infection\(^6\), and developmental defects of viviparity\(^9,21\). Approximately 70 families suffering from Alport's syndrome have been known since Sato et al. first reported it in 1962 in Japan\(^22\). The pathogenesis of Alport's syndrome is different from that of chronic glomerulonephritis and remains to be resolved, although the histological pattern of the kidney is consistent with the latter.

We have described an association of Alport's syndrome with retinitis pigmentosa sine pigmento, which has not been reported until now.

ACKNOWLEDGMENTS: We would like to thank Dr. Hiroyuki Shimada for evaluating the pathological changes of the patient.

REFERENCES

17) Sarles HE, Rodin AE, Poduska PR, Smith GH, Fish JC and Remmers AR Jr: Here-
A Case of Alport's Syndrome with Retinitis Pigmentosa sine Pigmento


