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THE ASSOCIATION BETWEEN HENOCH – SCHÖNLEIN SYNDROME AND RENAL AMYLOIDOSIS: A PROPOSAL OF A PATHOGENIC MECHANISM*

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SUMMARY: Tınaztepe K, Güçer Ş, Bakkaloğlu A, Tınaztepe B. (Nephropathology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The association between Henoch-Schönlein syndrome and renal amyloidosis: a proposal of a pathogenic mechanism. Turk J Pediatr 1993; 35: 249-256.

The clinicopathological analysis of 250 pediatric cases that had been tissue-diagnosed with renal amyloidosis revealed three patients associated with Henoch-Schönlein syndrome (HSS). The renal biopsies revealed AA-type amyloidosis in all three cases. Case 2 displayed focal and segmental proliferative glomerulonephritis in the same renal biopsy. No evidence of well-known diseases and / or conditions for the development of AA-type amyloidosis except for familial Mediterranean fever (FMF) existed in these particular cases. On the other hand, the frequency of the association between FMF and HSS has been reported extensively in the literature; thus, common etiological factors can be considered. The mechanism involved in amyloid deposition in these cases may be related to HSS-associated chronic antigenemia and / or FMF through a mechanism that is, to date, unknown. Further studies are needed to clarify this causal relationship. *Key words: Henoch-Schönlein purpura, renal amyloidosis, familial Mediterranean fever, childhood.*

Amyloidosis refers to a group of diseases characterized by an accumulation of an extracellular eosinophilic and hyaline subtance in various organs[1]. Though it is a relatively rare disease, renal involvement is frequent and is the major cause of death[1]. Cases of childhood amyloidosis are usually secondary to chronic inflammatory and infective disorders and familial conditions, many of which have been extensively studied[2,3]. On the other hand, there also reports of diseases rarely associated with amyloidosis which should be investigated[4-6]. In the majority of these diseases, chronic antigenic stimulation is most likely one of the causative factors in the complex pathogenesis of AA-type amyloidosis.

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The aim of this study is to present three cases with Henoch-Schönlein syndrome (HSS) and renal amyloidosis determined from investigated cases of tissue-diagnosed renal amyloidosis and biopsy-proven Henoch-Schönlein nephritis, and to discuss possible mechanisms and the relationship involved in the amyloidogenesis of this association.

Material and Methods

Three patients were found to have Henoch-Schönlein syndrome and renal amyloidosis during the analysis of 250 tissue-diagnosed renal amyloidosis and 38 biopsy-proven Henoch-Schönlein syndrome pediatric cases between 1966 and 1992 in the Pathology Department of Hacettepe Children's Hospital. Clinical charts and all pathological materials were used in the diagnostic evaluation. The diagnosis of HSS was based on the presence of at least two of the four criteria recommended by the American College of Rheumatology[7] :

1) Palpable purpura.
2) Age below 20 years at onset.
3) Abdominal pain (bowel angina).
4) Microvasculitis with granulocytic infiltration in the biopsy.

Renal biopsies from all three patients, were available while in Case 2, liver and lesional skin biopsies were also available. For light microscopic examination, renal tissue sections were stained with hematoxylin and eosin (HE), periodic acid Schiff (PAS), Jones' silver, Masson's trichrome, trichrome light green and Congo-red stains. The presence of amyloid was confirmed in Congo-red stained sections by demonstration of apple-green birefringence under polarized light. In all cases, AA-type amyloidosis was confirmed by potassium permanganate reaction[8].

The clinical signs and some pertinent laboratory findings of these three cases are presented in Table I.

Case 1

A 12-year-old girl was admitted to the hospital with the complaints of swelling of the hands, feet and eyelids. Four years earlier, she was diagnosed with HSS; she presented then with abdominal pain and skin lesions which were interpreted as palpable purpura as she began to experience intermittent episodes of fever, arthralgia and swelling of the joints. During the last eight months, she developed edema of the eyelids and feet.

Physical examination revealed blood pressure of 120 / 90 mmHg and pitting edema in both legs. The liver was palpated 2 cm and the spleen 1 cm below the costal margin.

Laboratory examination revealed a hemoglobin of 9.2 g / dl, white blood cell count 12,200 / mm^3, erythrocyte sedimentation rate (ESR) 140 mm / h total serum

Table I: Pertinent Clinical and Laboratory Data of Three Patients with Henoch-Schönlein Syndrome and Renal Amyloidosis

	CASES		
	1	2	3
Age (year) / sex	12, Female	11, Male	16, Male
Edema	+	+	+
Abdominal pain	+	+	++
Palpable purpura	+ (past history)	+ (on admission)	+ (past history)
Arthralgia	+	+	+
Hepatomegaly	+	+	–
Splenomegaly	+	+	–
Hematuria	–	–	+
Hypertension	–	–	+
ESR (mm / hour)	140	110	54
Hemoglobin (g / dl)	9.6	8.6	15
White blood cell count (per mm^3)	12000	8000	13600
BUN (mg / dl)	46	12	10
Creatinine (mg / dl)	–	0.6	0.8
Total protein (g / dl)	4.1	4.4	5.2
Albumin (g / dl)	2.0	2.3	1.6
Cholesterol (mg / dl)	236	280	134
Creatinine clearance (ml / min / 1.73 m^2)	–	46	91
Urinary loss of protein (g / 24 hours)	–	4.9	3.5
Renal biopsy	Amyloidosis AA-type	Amyloidosis AA-type and FSPGN*	Amyloidosis AA-type
Liver biopsy	–	Amyloidosis AA-type	–
Skin biopsy	–	LCV**	–

* FSPGN: Focal and segmental proliferative glomerulonephritis.
** LCV : Leukocytoclastic vasculitis.

proteins 4.1 g / dl, serum albumin 2.0 g / dl, cholesterol 236 mg / dl, and blood urea nitrogen (BUN) 46 mg / dl. Urinalysis showed proteinuria but no glucose. The urinary sediment contained 2-3 leukocytes as well as hyaline and granular casts. A diagnosis of amyloidosis was established by renal biopsy.

Case 2

An 11-year-old boy was admitted to the hospital for evaluation of joint pain, purpuric lesions in the gluteal areas and on the limbs, and edema of the feet. He had a six-year history of transient attacks of pain involving the ankles, knees and hips. During the ten days, before hospital admission, he began to experience painful swelling of the wrists, ankles and knees, and developed a purpuric rash in the gluteal areas and on the limbs.

Physical examination revealed a blood pressure of 100 / 70 mmHg. Painful pitting edema was noted in the fingers, wrists, ankles and knees. Palpable purpura was present on both legs and in the gluteal areas. The liver was palpable 4 cm and the spleen 2 cm below the costal margin.

Laboratory examination revealed a hemoglobin of 8.6 g / dl, white blood cell count 8000 / mm^3, ESR 110 mm / h total serum proteins 4.4 g / dl, serum albumin 2.1 g / dl, cholesterol 280 mg / dl, total lipids 1120 mg / dl, BUN 12 mg / dl, creatinine 0.6 mg / dl, and creatinine clearance 46 ml / min / 1.73 m^2. Tests for HBsAg, antinuclear antibody and rheumatoid factors were all negative. Urinalysis showed proteinuria, a specific gravity of 1020, hyaline and granular casts, and fat bodies in the sediment.

Lesional skin biopsy revealed the characteristic appearance of leukocytoclastic vasculitis (LCV). Liver biopsy showed fatty changes with AA-type amyloid deposition on the vascular walls. The kidney biopsy revealed AA-type renal amyloidosis and additional focal segmental proliferative glomerulonephritis. Colchicine therapy at a dose of 0.25 mg / day was initiated, and the patient was discharged on the 36th day of hospitalization. Five months later, he was still on colchicine with pretibial pitting edema and persistent proteinuria. One year after discharge, he died at home.

Case 3

A 16-year-old boy was referred to the hospital because of left knee pain, edema of the feet, and proteinuria. A diagnosis of HSS had been established ten years prior to hospital admission, at which time the patient had presented with abdominal pain, palpable purpura and arthralgia. He was followed up at regular intervals. Three days prior to this hospital admission, the patient developed pain in his left knee and slight swelling of the feet. Physical examination was unremarkable except for pitting edema at the ankles. His blood pressure was 110 / 70 mmHg on admission.

Laboratory examination revealed a hemoglobin of 16 g / dl, white blood cell count 9400 / mm^3, ESR 77 mm / h total serum proteins 5.2 g / dl, serum albumin 1.6 g / dl, BUN 10 mg / dl, creatinine 0.6 mg / dl, cholesterol 224 mg / dl, total lipids 458 mg / dl, and creatinine clearance 91 ml / min / 1.73 m^2. Urinalysis showed proteinuria with 3-4 leukocytes and 1-2 erythrocytes per high-power field.

On the second day of admission, a renal biopsy was performed to determine the cause of the proteinuria, and a diagnosis of renal amyloidosis was established. The patient was discharged on the tenth day of hospitalization and colchicine therapy was started. In the third year of follow-up, the child was noted to be hypertensive and was treated medically. Ten years later, he was in good health and had nearly normal renal function.

Renal Biopsy Findings

On light microscopic examination, Case 2 revealed a segmental deposition of amyloid in the glomeruli, while diffuse amyloid depositions of the glomeruli were present in Case 1 and 3. AA-type amyloidosis was demonstrated in all cases with potassium permanganate reaction. Additionally, in Case 2 the glomeruli displayed varying degrees of focal and segmental mesangial cell proliferation. Between these proliferative changes, small masses of amyloid deposits in the mesangial areas were easily recognized (Fig. 1).

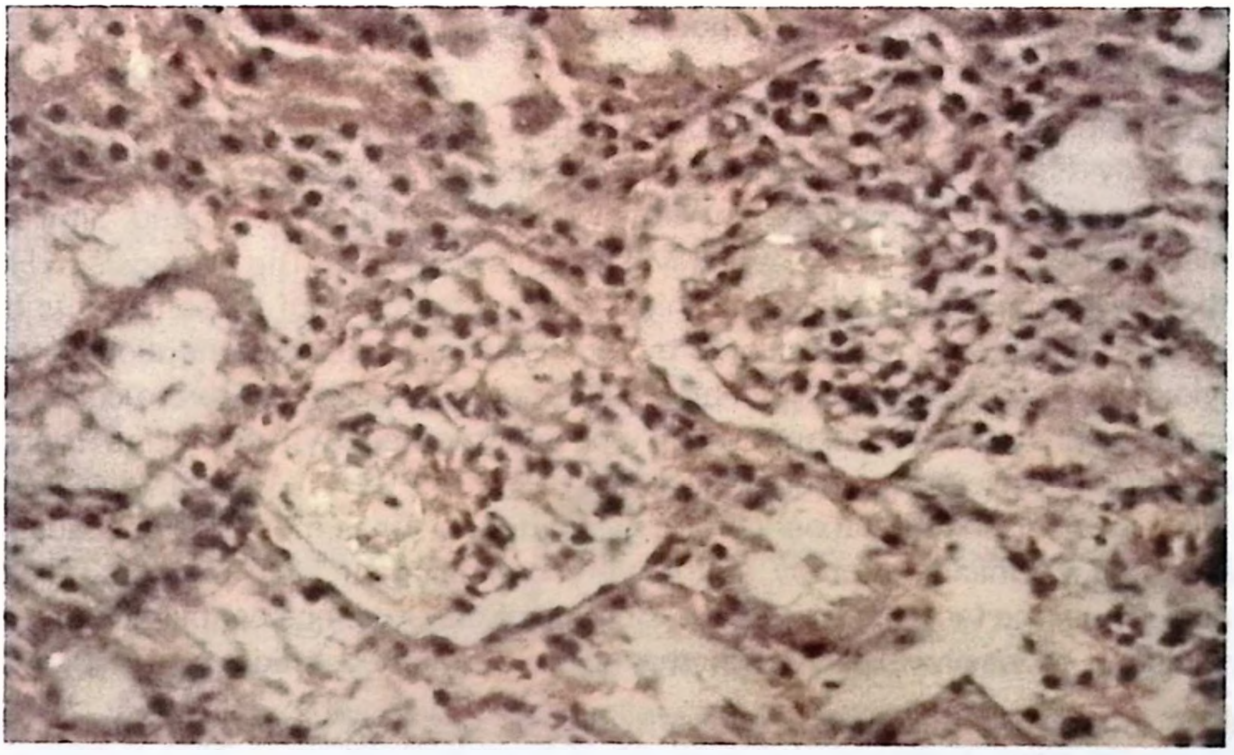

Fig. 1: Spicule-type minute masses of amyloid depositions showing apple-green birefringence and varying degrees of mesangial proliferation are seen in the glomeruli under partially polarized light (Congo-red stain, x 250).

Discussion

Henoch-Schönlein syndrome (HSS) is a type of microvasculitis which mainly involves the skin, gastrointestinal tract and kidneys[9]. Although it can occur in adults, it is a common childhood disease[10]. Renal involvement is the most serious complication and varies from minimal glomerular involvement to focal and diffuse proliferative glomerulonephritis[11]. On the other hand, renal amyloidosis is a rare disease in childhood and is associated mostly with juvenile rheumatoid arthritis, chronic infections and familial Mediterranean fever (FMF)[3,12-14].

In our earlier study of a pediatric series of 174 cases with renal amyloidosis, we found that FMF was the primary disease in the majority of cases (48%), and a minority of cases had juvenile rheumatoid arthritis (6.9%) and chronic suppurative infections (2.8%). In 32 percent of the cases, the underlying disease as a cause of AA-type renal amyloidosis was not clearly demonstrated[14]. However, in the latter cases it was concluded that phenotype II FMF may have been an underlying disease. Overall in 80 percent of the above-mentioned series, FMF may have been the main cause of renal amyloidosis.

Recently, several isolated cases of diseases demonstrated to be associated with renal amyloidosis have been reported[4,6]. On the other hand, until now an association between HSS and biopsy-proven renal amyloidosis has not been presented in the literature, though the association of Henoch-Schönlein syndrome and FMF has been reported[15-17]. Flatau et al[16], described eight cases of FMF with severe HSS. The authors made the diagnosis of HSS on the basis of clinical findings.

Skin biopsies of four patients and kidney biopsies of two patients were available in their study. Focal mesangial proliferative glomerulonephritis was seen in the two kidney biopsies, but no evidence of amyloid deposition was mentioned. Similarly, Schlesinger et al[17], reported seven FMF patients with HSS. The diagnosis of HSS in their series was based only on clinical findings, and one of these patients had proteinuria which was not evaluated by renal biopsy. There is no mention of renal amyloidosis in these studies or in previous reports, possibly due to the colchicine therapy given to FMF patients. It is well-documented that colchicine therapy prevents the development of amyloidosis[18]. If FMF is the causative factor in amyloidogenesis in HSS, absence of amyloid deposition is most likely because of the use of colchicine therapy at the very beginning of FMF patients' clinical course. Thus, the fact that there is no mention of the presence or absence of renal amyloidosis is easily explained in the above-mentioned studies.

Furthermore, in large series, renal amyloidosis has never been reported to be associated with HSS[19,20]. A pathogenic mechanism, chronic antigenemia involving immune complexes such as IgA, viral, bacterial and food antigens, as well as drug-related immune complexes, can play a role in triggering the

development of renal amyloidosis as it does in Henoch-Schönlein nephritis[9,11]. However, many types of chronic antigenemias are apparently not strong enough to cause amyloidosis, as there have been no reports of amyloidosis associated with HSS.

Kidney biopsy of Case 2 of our study showed focal and segmental endocapillary proliferative changes in the glomeruli, which is an unusual finding in renal amyloidosis[1]. The glomerular changes we observed were caused by both amyloidosis and Henoch-Schönlein nephritis. On the other hand, some of the overlapping findings of HS purpura and FMF appeared to be unrelated to FMF in Cases 1 and 3, since there was no clinical and familial history of FMF. The development of renal amyloidosis in these patients could be related to phenotype II FMF, because the patients exhibited no clinical findings of FMF. Thus, amyloidosis represents the initial feature of this disease. It is also possible that if chronic antigenemia, which is present in HSS, is a causative predisposing factor in the development of renal amyloidosis, it could be an accelerating and / or summation factor in amyloidogenesis in type-II FMF patients who are naturally prone to developing renal amyloidosis.

In conclusion, our cases presented the association of HSS with FMF-related renal amyloidosis. To our knowledge, these are the first cases of biopsy-proven renal amyloidosis associated with HSS to be reported in the literature. To enlighten these speculations, further studies on a molecular basis could provide the primary field of research.

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