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# *Glomerular basement membrane collagen deposits in nail patella syndrome a typical but not specific finding?*

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**SUMMARY**

*Glomerular basement membrane (GBM) collagen deposits have been considered pathognomonic of Nail-Patella syndrome (NPS). A case of association of typical renal lesions of the NPS, without nail and osseous manifestations, with a crescentic glomerulonephritis is reported. Based on the ultrastructural findings of this case and on the reexamination of 360 non-selected renal biopsies, evidence is produced in support of the non-specific nature, although typical when in the GBM, of those fibrillar collagen-like deposits.*

Key words: ***Nail-Patella syndrome. Glomerular basement membrane-collagen deposits.***

**DEPOSITOS DE COLAGENO EN LA MEMBRANA BASAL GLOMERULAR EN EL SINDROME UÑA-ROTULA. ¿UN HALLAZGO TIPICO PERO INESPECIFICO?**

**RESUMEN**

*Los depósitos de colágeno en la membrana basal glomerular se han considerado patognomónicos del síndrome uña-rótula. Se describe un caso de asociación de lesiones renales típicas de este síndrome sin manifestaciones óseas ni ungueales, con una glomerulonefritis extracaspilar. Sobre la base de los hallazgos ultraestructurales de este caso y del examen de otras 360 biopsias renales no seleccionadas se aportan evidencias en favor de la naturaleza inespecífica de estos depósitos fibrilares de aspecto de colágeno en la membrana basal glomerular.*

Palabras clave: ***Síndrome uña-rótula. Depósitos de colágeno en la membrana basal glomerular.***

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## Introduction

Nephropathy associated to Nail-Patella Syndrome (NPS) is an entity of genetic basis characterized by a peculiar alteration of the glomerular basement membrane with deposition of collagen-like fibrils[1,2].

These deposits by the localization and morphologic characteristics have been considered pathognomonic[3] in the diagnosis of the entity, even in the absence of extrarenal manifestations[4]. In this paper a necropsy study of a new observation of a nephropathy with glomerular basement membrane deposits of collagen-like material but without nail and osseous abnormalities is presented. In order to evaluate the frequency and appearence of morphologic alterations similar to the NPS, the glomerular ultrastructure of a non-selected control group of 360 renal patients is reviewed.

## Case Report

A 60-year old woman was admitted to Hospital S. João with chronic renal failure, aggravated two weeks before. She was pale and apyretic and presented dyspnea, orthopnea, nausea, vomits, hemoptoic expectoration, hematuria and pretibial edemas. Respiratory frequency was 44 cycles/minute. Pulmonar auscultation revealed prolonged espiration and crepitations, more abundant in the right base. Cardiac auscultation was normal, but for a grade 3/6 holosystolic murmur which could be better heard in the apical focus. Radial pulse frequency was 108 cycles/minute and rythmic. Blood pressure was 150/120 mmHg. The physical examination was otherwise negative especially for bone and nail changes.

Laboratory investigations were as follows: hemoglobin level, 8.1 g/dl; hematocrit reading, 28 %; white blood cell count, 11.5 × $10^9$/L (N-86.5; E-1.0; B-0.0; L-10.5; M-2.0); BUN level, 74.8 mg/100 ml (12.4 mmol/L); glicose level, 160 mg/100 ml (8.9 mmol/L); ionogram: $Na^+$-138 mEq/L (138 mmol/L); $K^+$-6,6 mEq/L (6,6 mmol/L); $Cl^-$-105 mEq/L (105 mmol/L); on admission urinalysis revealed proteinuria (3+), many RBC and WBC, and few hyaline and granular casts.

Although supportive treatment (Aminofilin, Furosemide, Digoxin, Oxigenotherapy) was performed, the patient died five hours after admission due to acute pulmonar edema before being submitted to hemodyalisis treatment.

An autopsy study was performed only 24 hours after death (for legal reasons). It was not possible to obtain a consistent familiar history.

The ultrastructural study of the kidneys showed collagen glomerular basement membrane deposits described as typical of the renal lesions in the Nail-Patella syndrome (NPS)[3]. In order to evaluate the frequency of glomerular deposits similar to those observed in NPS, the ultrastructural features of 360 non-selected kidney biopsies were re-examined. In this study particular attention was paid to detect deposits of collagen-like material in the glomerular basement membranes.

## Results

### 1. *Necropsy study*

The kidneys (120 g R/140 g L) presented smooth and pale cortical surface dotted by petechias and congested medullae. By light microscopy 75 % of the glomeruli were hypercellular with striking crescentic formation in Bowman's space (fig. 1). Fibrin and few necrotic areas were present in the crescents. Some glomeruli were totally replaced by hyaline connective tissue. The tubules showed variable degrees of cellular injury and contained hyaline and pigmented granular casts some of them with RBC. There was marked interstitial edema and focus of inflammatory mononuclear cells.

The electron microscopic study disclosed the epithelial characteristics of the glomerular crescents and sclerotic glomeruli with hyalinization. The less damaged glomeruli showed thickening of the basement membrane containing fascicles of fibrous long-spaced collagen-like fibrils with a periodicity of 816 Amgstrons (A) (figs. 2, 3 and 4). These fascicles, also present in the mesangium, had a diameter varying between 1407 A and 4611 A. Some had tapered ends, assuming a structure similar to that described by Luse[5] (fig. 2, inset). Electron dense deposits of immune-type were not found in the glomeruli observed.

Bilateral pulmonar edema, pleural effusions (500 $cm^3$ each side) and moderate subcutaneous edema were the other significant alterations revealed by the autopsy.

### 2. *Study of the control group*

The re-examination of the glomerular ultrastructure in the control group (Table I) revealed glomerular deposits

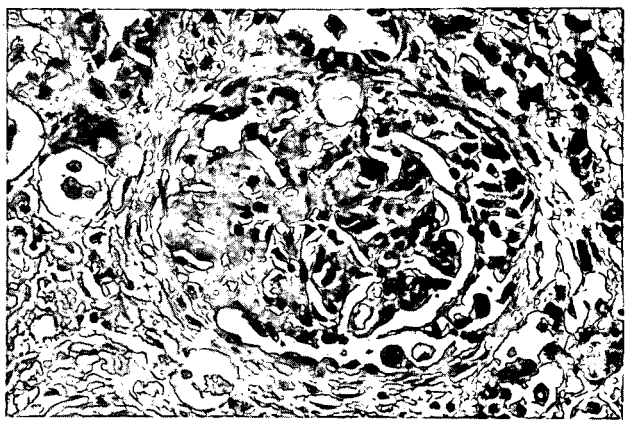

*Fig. 1.—Glomerular lesions: proliferation of epithelial cells with crescent formation and segmental sclerosis. (HE × 300).*

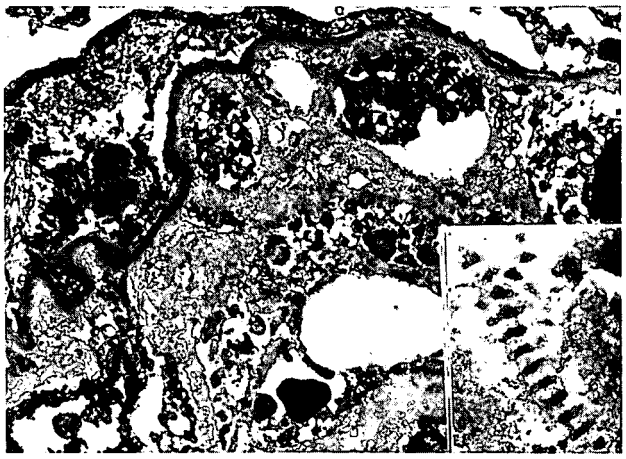

*Fig. 2.—Glomerular basement membrane (GBM) with collagen fascicles. (× 7.500). Inset-collagen fascicle in GBM with Luse body structure. (× 39.600).*

*Fig. 3.—Glomerular capilar: collagen-fascicles within GBM. (× 12.000).*

**Tabl I.** Ultrastructural Collagen-like Deposits in Non-Selected Renal Diseases

| Glomerular diseases | N.° of cases | Collagen-like deposits n.° (%) | Diameter A | Localization |
|---|---|---|---|---|
| Lipoid nephrosis | 6 | 0 | — | — |
| Lipoid nephrosis with minimal proliferation | 17 | 0 | — | — |
| Focal segmental glomerulosclerosis | 15 | 0 | — | — |
| Acute diffuse proliferative | 10 | 0 | — | — |
| Crescentic proliferative | 4 | 0 | — | — |
| Membranous | 27 | 1 (3.70) | 378 | Mesangium |
| Mesangial proliferative | 121 | 1 (0.83) | 294 | Mesangium |
| IgA Glomerulopathy | 21 | 1 (4.76) | 410 | Mesangium |
| Membranoproliferative | 32 | 0 | — | — |
| Focal proliferative | 9 | 0 | — | — |
| End Stage nephritis | 9 | 0 | — | — |
| Alport's syndrome | 5 | 1 (20.00) | 417 | Glomerular basement membrane |
| Systemic lupus erythematous | 41 | 0 | — | — |
| Goodpasture syndrome | 1 | 0 | — | — |
| Amyloidosis | 13 | 1 (7.69) | 89 | Mesangium |
| Diabetic nephropathy | 3 | 0 | — | — |
| Multiple myeloma | 6 | 1 (16.67) | 192 | Mesangium |
| Others | 20 | 0 | — | — |
| Total | 360 | 6 (1.67) | | |

of collagen-like material in six cases. In five cases these deposits were located in the mesangial area and in one case the relationship between the fibril deposits and the basement membrane was close (fig. 5). This last case was a typical case of Alport's Syndrome (AS). The diameter of the fibrils observed in this group was between 89 A and 417 A.

## Comments

Collagen-like fibrils have been observed in the glomerular mesangium associated with different experimental and clinical pathological situations, such as Masugi nephritis, Diabetis, S.L.D., Amyloidosis and others[1,6-8]. However, these deposits have been observed in basement membranes only in the NPS. Although this entity had been associated with AS, the clinical and pathological characteristics were sufficiently distinct to consider it as an autonomous entity[9]. Moreover renal lesions, with or without clinical and analytical symptoms or signals, have not always been present in the NPS[3,6]. Cases with typical renal lesions and without nail and osseous manifestations have also been reported[4]. This case could represent, as the cases reported by Sabnis, an incomplete expression

*Fig. 4.—Detail of Fig. 3 showing well defined collagen fibrils near the lumen of the glomerular capilar. (× 18.000).*

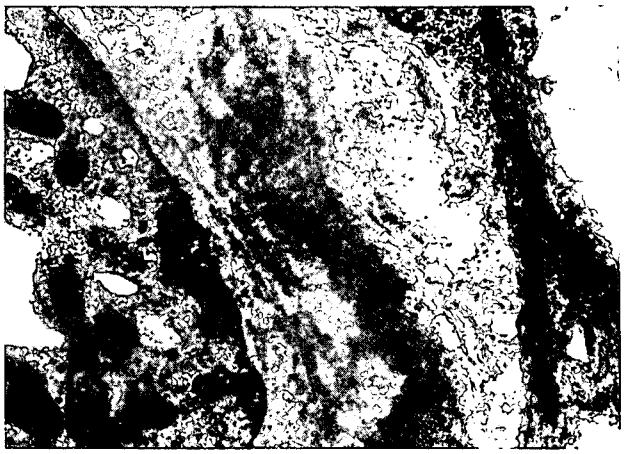

*Fig. 5.—Alport syndrome: collagen-like fibrils in close proximity to GBM. (× 30.000).*

of the NPS. Alternatively, in our opinion, it could be an example of the non-specificity of collagen deposition in the glomerular basement membrane, as also suggested by others[10,11].

This case also exhibits some particular characteristics. The advanced age of the patient and the evolution of the renal lesions to renal failure in the form of a crescentic glomerulonephritis (CG) are not common. A rare case of association of NPS with Goodpasture syndrome has been described[12]. However, as far, the association of NPS with CG has never been reported. It is tempting to speculate that the abnormal basement membrane, observed in this case, could have played an important role in the development of the crescentic glomerulonephritis, as suggested by others in cases of glomerular basement membrane lesions[13]. Moreover the morphologic type of the fibrillar deposits very similar to long-spaced collagen described by Luse[5] have to the best of our knowledge never been reported.

The revision of the 350 glomerular lesions confirms that, although the collagen-like deposits were found to be variable in calibre, they were not uncommonly associated with different pathological situations. On the contrary, only AS case showed deposits in the glomerular membranes (fig. 3) which were very similar to those of the NPS documented by Taguchi T. et al.[3].

These facts support the view that, although collagen-like deposits in close proximity to the basement membrane are highly suggestive of NPS when localized in the renal glomerulus, they are not specific of any type of pathology but are the expression of alterations in the basement membrane metabolism[2,9] including it's collagen precursors. This morphologic alteration can be observed in different situations such as tumors, namely schwannomas[5] and myoblastomas[7], and in pathology of genetic bases such as AS and NPS, with more or less renal and extra-renal involvement and variable characteristics of collagen deposits.

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