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*Original Article*

# Dense Deposit Disease: A 29-Years Electron Microscopy Experience

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## Abstract

**Introduction**: Dense Deposit Disease (DDD) is a devastating renal disease that leads to renal failure within 10 years of diagnosis in about half of affected patients. In this study, we evaluated the relative prevalence and pathological features of DDD diagnosed at our center over a 29 years period.

**Methods**: We reviewed the clinical and pathological features of all cases of DDD diagnosed at the Electron Microscopy Unit of Ain Shams University (ASUSH) between January 1983 and December 2011.

**Results**: From a total of 3283 renal biopsies, 33 (1%) were diagnosed with DDD (10 children and 23 adults). Nephrotic syndrome was the predominant clinical presentation of DDD (51.5%), and was commoner in children than adults (80% vs. 43%, p=0.03). Capillary wall thickening was seen in all cases (100%). Crescents were more commonly seen in children than adults (70% vs. 21.7%, p=0.008) while interstitial fibrosis was more commonly seen in adults (78.3% vs. 40%, p=0.03). The commonest histological pattern seen under light microscopy was membranoproliferative (27.3%), followed by crescentic (21.2%), membranous (21.2%), diffuse proliferative (18.2%), lobular (6.1%) and mesangial proliferative (6.1%) patterns. Immunohistochemistry was available for 25 cases and showed intense linear staining for C3 along capillary walls. Electron microscopic examination revealed glomerular basement membrane (GBM) thickening and intra-membranous and tubular basement membrane deposits in all cases (100%).

**Conclusion**: DDD is a rare disease in Egypt, found in only 1% of renal biopsies. Pathological features of the disease differ between adults and children; children have predominantly glomerular damage whereas tubule-interstitial lesions are more often encountered in adults.

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## Introduction

Dense deposit disease (DDD) is one of the rare glomerular diseases. It was first described by Berger and Galle (1963) as a subtype of membranoproliferative glomerulonephritis. The disease was specifically diagnosed by electron microscopy via the presence of intra-membranous electron dense deposits principally in the glomerular basement membrane (GBM) [1].

The pathogenesis of DDD is controversial; some authors described the deposits as an oligosaccharide substance rather than immune complex deposits [2], others claimed that immunity had a pivotal role in the formation of the deposits via C3 nephritic factor (C3NeF), which is an IgG that might act as an autoantibody against the C3 convertase component of the alternative complement pathway. C3NeF was revealed in the sera of 80% of DDD patients and it is still unknown whether this factor is the trigger or the consequent exacerbating factor for the disease process [3].

Clinically, the age presentation of DDD is variable. Some authors described DDD mostly affecting children between 5 to 15 years of age [4]. Others reported the disease as affecting children and young adults with no sex predilection [3, 5]. It can produce a variety of signs and symptoms including proteinuria and/or hematuria, nephrotic syndrome or acute nephritic syndrome. Systemic involvement has been frequently encountered with DDD, including acquired partial lipodystrophy (APL) and ocular involvement in the form of Drusen's deposits. The latter might cause serious retinopathy in 10% of patients. Prognosis of DDD is variable; half of

the patients progress to end stage renal disease within 10 years of diagnosis.

Renal biopsy usually shows heterogeneous histological patterns in light microscopy [4]. However, certain renal biopsy findings rather than clinical or laboratory features could be helpful in determining patients who are prone to experience progressive renal insufficiency. These histological indicators include the presence of mesangial deposits, the degree of mesangial proliferation and glomerular sclerosis, and the presence of crescents [6].

The aim of this study was to highlight the prevalence of dense deposit disease (DDD) in Egypt by reviewing cases diagnosed at the Electron Microscopy Unit of Pathology Department at Ain Shams University Specialized Hospital (ASUSH) and to study the difference, if any, in the clinical and pathological presentations of the disease among children and adult patients.

## Methods

This study included all renal biopsies received at the Electron Microscopy unit of Ain Shams University Specialized Hospital between January 1983 and December 2011. This unit is one of very few diagnostic electron microscopy units in Egypt. The study was approved by the local ethical institutional review board.

We analyzed all cases diagnosed as DDD. Demographic, clinical, and laboratory data were retrieved from the pathology records. Patients ≤16 year of age were considered as children. Light microscopy slides, including conventional H&E sections, PAS, Reticulin and Masson Trichrome specially stained sections, together with immunologic data, and electron microscopy photographs were independently reviewed by four nephropathologists who were blinded to the clinical history and previous diagnoses.

The relation between patients' age category and different clinical and pathological features was analyzed using the Chi-square and Fisher exact tests. Statistical significance was assumed at $p < 0.05$.

## Results

A total of 3283 renal biopsies were recorded during the study period, 33 of which were reported as cases of DDD. Thus, DDD represents 1% of the total renal biopsies examined over the 29 years of the study.

Of those 33 DDD cases, 19 were males (57.6%) and 14 were females (42.4%), with a male: female ratio of 1.4:1. The age of patients ranged from 3-74 years with a mean age of 28.5 years. DDD cases were divided into two groups; the pediatric group included 10 cases, 6 males and 4 females, with a mean age of 9 years (range 3-16). The adult group comprised 23 cases, 13 males and 10 females, with a mean age of 36.9 years (range 18-74).

Clinical presentation of studied patients is shown in Table-1. Nephrotic syndrome was the commonest clinical presentation and was significantly more common among pediatric patients. Reported associated conditions included Goodpasture's syndrome, chronic bronchitis, hematemesis, pneumonia, diabetes mellitus type II, cryoglobulinemia, urinary bilharziasis and uric acid stones. None of the medical records included a description of acquired partial lipodystrophy (APL). C3 level and C3 nephritic factor results were available in six children and 14 adults; C3 level was decreased in five of the six children (83%) and 10 of the 14 adults (71.4%). C3 nephritic factor was detected in 4/6 children (66.7%), and 8/14 adults (57.1%).

The mean number of glomeruli examined was 19±2. Light microscopy findings of studied cases are shown in Table-2. Capillary wall thickening was seen in all cases followed by tuft hypercellularity and mesangial sclerosis. Crescents were significantly more common in pediatric age group (70% vs. 21.7%, p=0.008). Six histological patterns were identified; membranoproliferative, crescentic, acute proliferative and exudative, membranous glomerulonephritis like pattern, pure mesangial hypercellularity (focal and segmental or diffuse), and lobular glomerulonephritis (Figure-1). Membranoproliferative dense deposit disease was characterized by endocapillary proliferation producing a mesangial lobular appearance. Crescentic dense deposit disease was characterized by the presence of crescents in more than 50% of the glomeruli available for examination. Membranous pattern was defined by the more or less normal glomerular cellularity, with thickened capillary walls. Diffuse proliferative and exudative dense deposit disease showed diffuse glomerular hypercellularity due to endocapillary proliferation with prominent neutrophilic infiltration and occlusion of most capillary lumens. Lobular pattern was defined by the presence of an accentuated lobular pattern, with sclerotic mesangial nodules resembling nodular diabetic glomerulosclerosis. Mesangial proliferative dense deposit disease was characterized by focal segmental mesangial hypercellularity. The frequencies of different histological patterns are shown in Table-3. Tubulointerstitial findings and vascular changes seen under light microscopy are shown in Tables 4 and 5. Interstitial fibrosis was commoner in the adult group (78.3% vs. 40%, p = 0.03).

**Table-1: Clinical presentation of studied dense deposit disease (DDD) patients**

| Clinical Feature | Pediatric Group | Adult Group | Total |
|---|---|---|---|
| Nephrotic syndrome | 8 (80%)* | 10 (43.5%) | 18 (51.5%) |
| Hypertension | 4 (40%) | 5 (21.7%) | 9 (27.3% ) |
| Renal impairment | 2 (20%) | 6 (26.1%) | 8 (24.3%) |
| Hematuria | 3 (30%) | 4 (17.4%) | 7 (21.2%) |
| Proteinuria (sub-nephrotic) | 0 (0%) | 6 (26.1%) | 6 (18.2%) |
| Chronic renal failure | 0 (0%) | 3 (13%) | 3 (9.1%) |
| Acute renal failure | 1 (10%) | 1 (4.3%) | 2 (6.1%) |

* Difference between adults and pediatric groups is statisticaly significnat (p=0.03).

**Table-2: Light microscopic features of glomeruli in studied dense deposit disease (DDD) patients**

| Light Microscopy Feature | Pediatric Group | Adult Group | Total |
|---|---|---|---|
| Capillary wall thickening | 10 (100%) | 23 (100%) | 33 (100%) |
| Tuft hypercellularity | 8 (80%) | 17 (73.9%) | 25 (75.7%) |
| Mesangial sclerosis | 7 (70%) | 18 (78.3%) | 25 (75.7% ) |
| Neutrophils | 6 (60%) | 8 (34.8%) | 14 (42.4% ) |
| Loop obliteration | 5 (50%) | 8 (34.8%) | 13 (56.5% ) |
| Large glomeruli | 4 (40%) | 9 (39%) | 13 (56.5%) |
| Crescents | 7 (70%)* | 5 (21.7%) | 12 (36.4% ) |
| Mesangial expansion | 2 (20%) | 7 (30.4%) | 9 (27.3% ) |
| Accentuated tuft lobulation | 1 (10%) | 7 (30.4%) | 8 (24.2%) |
| Periglomerular fibrosis | 1 (10%) | 5 (21.7%) | 6 (18.2% ) |
| GBM splitting | 2 (20%) | 3 (13%) | 5 (15.2% ) |
| Lobular pattern | 0 (0%) | 3 (13%) | 3 (9.1% ) |
| Karyorrhexis | 0 (0%) | 0 (0%) | 0 (0%) |

GBM: glomerular basement membrane.

* Difference between adults and pediatric groups is statisticaly significnat (p= 0.008).

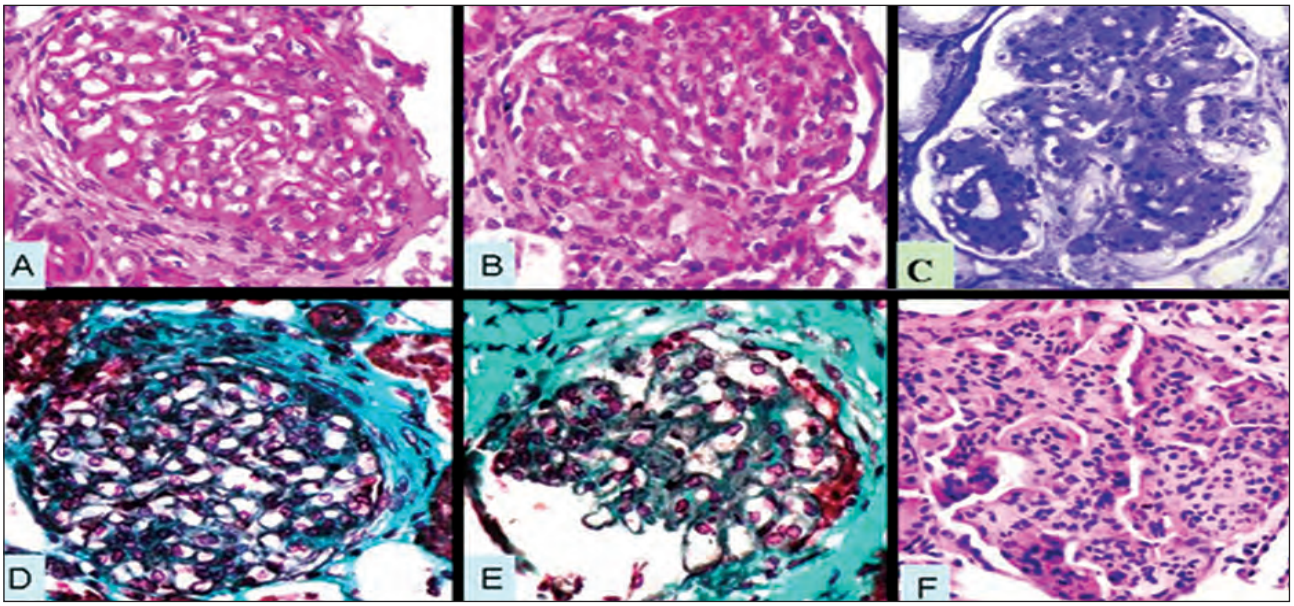
Immunohistochemistry staining was available in 25 cases only (20 adults and five children). It showed intense positivity of capillary walls for C3 in all cases, focal granular positivity was detected in tubular basement membrane in 15 cases (60%). Other immunoglobulin positivity was observed faintly in 15 cases (IgG; 7 cases, IgM; 6 cases, IgA; 2 cases).

Electron microscopic examination revealed glomerular basement membrane (GBM) thickening, intramemberanous and tubular basement membrane deposits in all cases (100%). Subendothelial, subepithelial, mesangial and Bowman's capsule deposits were found in smaller percentages. Effacement of epithelial foot processes was also found in some cases (Table-6, Figure-2).

## Discussion

Dense deposit disease (DDD) is a glomerular disease defined as transformation of the lamina densa of the GBM into a ribbon-like, highly electron-dense material under electron microscopy, which stains predominantly for C3 by immunofluorescence [5]. It is a rare disease

**Figure-1: Different morphologic patterns of studied dense deposit disease (DDD) cases**




(A) Membranous pattern (H&E x400) (B) Membranoproliferative pattern (H&E x400); (C) Lobular pattern (Toulidine blue x250); (D) Crescentic pattern (Masson trichome x400); (E) Mesangioproliferative pattern (Masson trichome x400); and (F) Diffuse proliferative exudative pattern (H&E x250).

that affects only two to three individuals per million populations [7].

The current study reports our experience with a series of 33 cases diagnosed by light microscopy, immunohistochemistry, and confirmed by electron microscopy as DDD. To our knowledge, this is the first study dealing with the clinicopathological features of patients with DDD in Egypt. In this study, cases of DDD represented 1% of the total renal biopsies received in ASUSH in the period from 1983 to 2011, and represented 10.3% of the total MPGN cases. This frequency is comparable to figures reported by other studies and confirms that DDD is a rare disease [1-14]. The major finding in this study is that light microscopy pattern was variable in DDD and membranoproliferative pattern was seen in only 27.1%. In addition, DDD produced more severe glomerular damage in children, while more interstitial fibrosis was seen in adults.

In this study, there was a slight male predilection. Nasr *et al* studied 32 cases of DDD in North America [5] and found a slight female predilection, while another study recorded male predilection in children [9]. In our study the majority of patients were adults, other studies showed that DDD was a disease of children and young adults, and less common in older age groups [8]. The higher percentage of adult and male patients in the current study might be related to different genetic and racial factors in the Egyptian patients.

Nephrotic syndrome was the commonest clinical presentation, seen in over half of the patients, with a higher frequency in pediatric patients. This could be explained on the basis of glomerular membrane structural changes of the lamina densa. The findings of hypertension and proteinuria are more or less similar to the results of Lu *et al* who studied 98 cases of adults and children with DDD. They found that the majority of patients presented with hematuria and proteinuria, and 50% of cases presented with hypertension [10].

Generally, about 50% of DDD patients progress to ESRD and require dialysis within 10 years of diagnosis [15, 16]. Various studies have suggested that factors predictive of progression to renal failure include: younger age at diagnosis, specific variants of renal pathology, elevated serum creatinine concentrations and proteinuria at time of diagnosis, initial presentation with nephrotic and nephritic syndromes, and >20% chronic renal damage on initial biopsy [5,13]. Early detection, monitoring, and treatment of the complications of chronic kidney disease (CKD) including hypertension, proteinuria, phosphorus and calcium dysregulation, and anemia were essential to delay progression to ESRD [17].

**Table-3: Histologic patterns of studied dense deposit disease (DDD) cases under light microscopy**

| Histologic Pattern | Pediatric patients | | | Adult patients | | | Total cases |
|---|---|---|---|---|---|---|---|
| | Males | Females | Total | Males | Females | Total | |
| Membranoproliferative | 2 | 1 | 3 (30%) | 2 | 4 | 6 (26.1%) | 9 (27.3%) |
| Crescentic | 2 | 2 | 4 (40%) | 2 | 1 | 3 (13%) | 7 (21.2%) |
| Membranous | 1 | 1 | 2 (20%) | 3 | 2 | 5 (21.7%) | 7 (21.2%) |
| Diffuse Proliferative | 1 | 0 | 1 (10%) | 5 | 0 | 5 (21.7%) | 6 (18.2%) |
| Lobular | 0 | 0 | 0 (0%) | 1 | 1 | 2 (8.7%) | 2 (6.1%) |
| Mesangial Proliferative | 0 | 0 | 0 (0%) | 2 | 0 | 2 (8.7%) | 2 (6.1%) |

**Table-4: Light microscopic features of renal tubules and interstitial tissue of studied dense deposit disease (DDD) cases**

| LM Features | Pediatric Group | Adult Group | Total |
|---|---|---|---|
| Tubular atrophy | 7 (70%) | 18 (78.3%) | 25 (75.7%) |
| Interstitial inflammation | 7 (70%) | 17 (73.9%) | 24 (72.7%) |
| Interstitial fibrosis | 4 (40%) | 18 (78.3%)* | 22 (66.7%) |
| TBM thickening | 2 (20%) | 2 (8.7%) | 4 (12.1%) |
| Tubulitis | 0 (0%) | 3 (13%) | 3 (9.1%) |
| Tubular cell degeneration | 2 (20%) | 1 (4.3%) | 3 (9.1%) |
| Interstitial edema | 0 (0%) | 1 (4.3%) | 1 (3%) |

TBM: tubular basement membrane.

* Difference between adults and pediatric groups is statisticaly significnat (p = 0.03).

In the current study, chronic renal failure was the first presentation in three patients; one female aged 22 years with membranoproliferative pattern, and two males aged 54, and 74 years with membranous pattern. Lu *et al* [10] reported that young females had a higher risk of developing chronic renal failure. Another study reported that end stage renal disease was related more to older age and higher creatinine level at diagnosis rather than the histological pattern [5]. Liu *et al* studied 12 children with DDD and described three cases with crescentic pattern [9]. In the current study there was a significant association between crescents formation and the pediatric age group, indicating that DDD produced more severe damage in children than in adults.

Habib *et al* [12] noted the similarity of dense deposit disease and membranoproliferative glomerulonephritis by light microscopy, and classified dense deposit disease as a variant of membranoproliferative glomerulonephritis (MPGN type II), although classic light microscopic features of membranoproliferative glomerulonephritis were present in only 25% of their series. Walker *et al* [13] and Sethi *et al* [14] also reported cases of DDD with different histological patterns. Similarly in our study, membranoproliferative pattern represented only 27.1% of cases, which supports the notion that DDD is likely to be a separate entity of renal diseases with variable histological patterns. The prognostic implication of the various histological patterns remains unanswered and need further longitudinal researches.

Our findings suggest that DDD could produce more severe tubulointerstitial damage in adults than in children. The higher incidence of renal impairment and failure found in adults compared to pediatric group could be attributed to the more severe tubulointerstitial damage. The determination of the severity of tubulointerstitial involvement in those patients is important for the planning of adequate treatment. Some authors suggested that, the use of angiotensin converting enzyme inhibitors could

**Table-5: Light microscopic vascular changes of studied dense deposit disease (DDD) cases**

| LM Features | Pediatric Group | Adult Group | Total |
|---|---|---|---|
| Hyalinosis | 2 (20 %) | 10 (43.5%) | 12 (36.4% ) |
| Intimal fibrosis | 2 (20 %) | 3 (13%) | 5 (15.2%) |
| Narrow lumina | 1 (10 %) | 3 (13%) | 4 (12.1%) |
| Perivascular inflammation | 0 (0 %) | 1 (4.3%) | 1 (3%) |

**Table-6: Electron microscopic changes of studied dense deposit disease (DDD) cases**

| EM Features | Pediatric Group | Adult Group | Total |
|---|---|---|---|
| GBM thickening | 10 (100%) | 23 (100%) | 33 (100%) |
| Intramembranous deposits | 10 (100%) | 23 (100%) | 33 (100%) |
| TBM deposits | 10 (100%) | 23 (100%) | 33 (100%) |
| Mesangial deposits | 3 (30%) | 4 (17.4%) | 7 (21.2%) |
| Bowman's capsule deposits | 2 (20 %) | 5 (21.7%) | 7 (21.2%) |
| Fusion of foot processes | 1 (10 %) | 4 (17.4%) | 5 (15.2%) |
| Subendothelial deposits | 1 (10 %) | 1 (4.3%) | 2 (6.06%) |
| Subepithelial deposits | 2 (20 %) | 0 (0%) | 2 (6.06%) |
| GBM spikes | 0 (0 %) | 0 (0%) | 0 (0%) |
| Interposed mesangial cytoplasm | 0 (0 %) | 0 (0%) | 0 (0%) |

GBM: glomerular basement membrane; TBM: tubular basement membrane.

reduce the degree of proteinuria and might ameliorate the severity of tubulointerstitial fibrosis [15-17].

## Conclusion

In conclusion, this study indicates that DDD is a rare disease in Egypt and can present over a broad age range. The disease shows heterogeneous clinical presentations and histological patterns.

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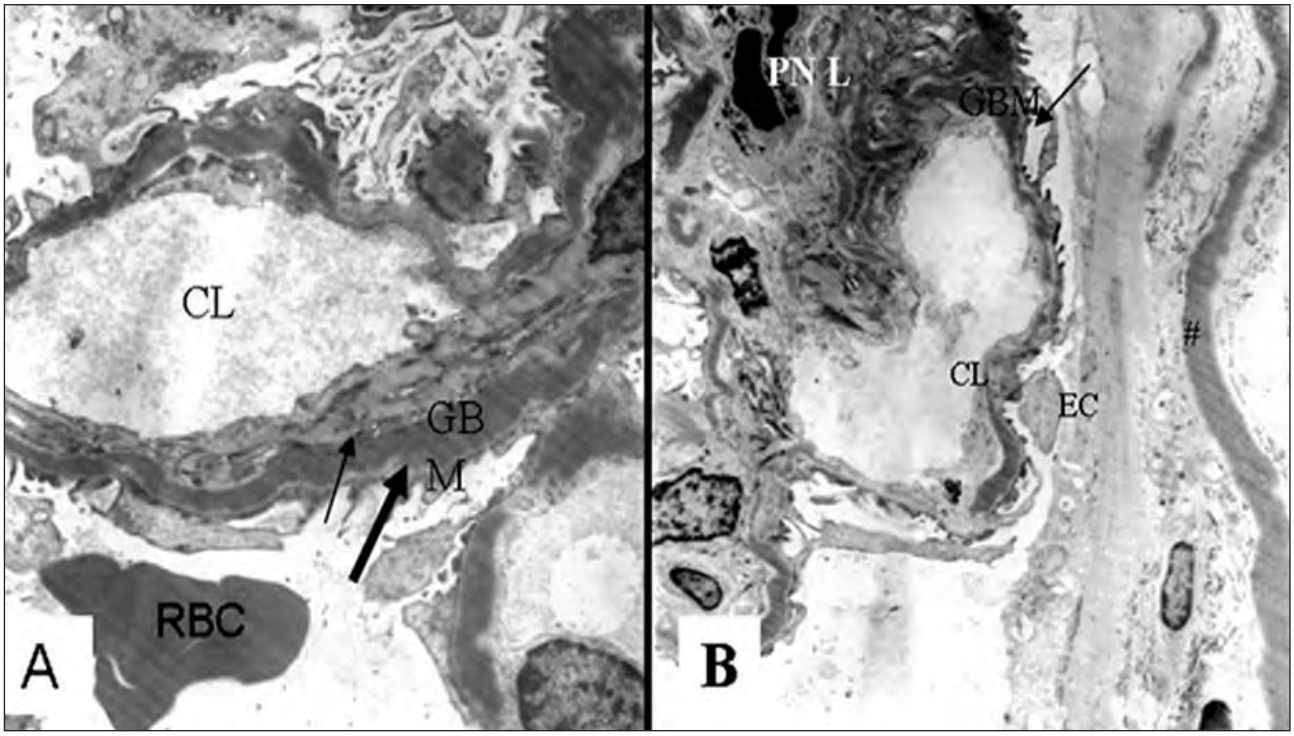
**Figure-2: Electron microscopic photograph of dense deposit disease.**




(A) Picture shows interrupted linear intramembranous electron dense deposits (thin arrow) within an irregularly thickened glomerular basement membrane (GBM). Effacement of epithelial cell (EC) foot processes is noted (thick arrow), and some RBCs are seen in the urinary space outside capillary lumina (CL). In (B) a neutrophil (PNL) is seen and linear deposits are also noted within tubular basement membrane (#) (Uranyl acetate and Lead citrate; A X3600, B X2800)

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