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Reporting and Interpreting Renal Biopsies – A Review Article

Anusha Anish [aΦ*], Hari S. Pillai [a#] and P. T. Annamalai [a†]

[a] PSM College of Dental Science & Research, Akkikavu, Thrissur, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Medical renal biopsy is an important tool in patient care in nephrology department. Systematic reporting of a renal biopsy eases the communication between the pathologist and the clinician, thereby improving patient care. H & E (Hematoxylin and eosin) sections alone cannot help to arrive at a diagnosis, immunofluorescence (IF), special stains and EM (electron microscopy) play important roles too. To arrive at an accurate diagnosis, an expert renal pathologist, who has a thorough knowledge of renal pathology as well as renal medicine is required to correlate tissue with clinical data. Although a lot of review articles regarding renal biopsies have been published, review of literature covering all aspects of renal biopsy are a few especially from India. In children the common cause of nephrotic syndrome is minimal change disease, which can only be confirmed with EM (diffuse effacement of foot processes). While the commonest cause of nephrotic syndrome in adults is membranous nephropathy which needs a combination of H & E (Thickened capillary loops), Silver stains (Spikes), IF (Fine granular staining of IgG & C3 in capillary walls) and EM (Subepithelial deposits). In terms of nephritic syndrome, the most common cause in children is post-streptococcal glomerulonephritis, which is diagnosed with H & E (Hypercellularity), IF (Coarse granular staining of IgG & C3 in capillary walls) and EM (Large subepithelial deposit). In adults, one of the most common causes of nephritic syndrome is rapidly progressive glomerulonephritis, which shows characteristic crescents in both H & E and special stains.

[Φ] Professor of Pathology & Deputy Research Director;
[#] Principal;
[†] Research Director;
**Corresponding author: E-mail: dranushaanish@gmail.com;*

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1. INTRODUCTION

For the accurate diagnosis of renal disease, renal biopsy is often essential. In addition, renal biopsy is frequently used to assess activity and chronicity, which is used to decide upon the appropriate therapy and to determine the prognosis [1]. A proper format is required to report renal biopsies so that all aspects are covered. Special stains supplement the light microscopy, especially Periodic acid–Schiff **(**PAS), Silver methenamine, Masson's trichrome and Congo red. It also helps to stain various components of the renal tissue [2]. Immunofluorescence is an irreplaceable technique which is used for accurate diagnosis in renal pathology, especially in diseases like IgA nephropathy (IgAN), C1q nephropathy (C1qN) and C3 glomerulopathy (C3G), which cannot be diagnosed without IF [3]. EM on the other hand must be done on all renal biopsies, but unfortunately, they are available only in tertiary or referral centres [4].

2. AIMS

The aim of the article was to review the literature with respect to the interpretation of renal biopsies. Also, articles linked to IF and EM was reviewed.

3. METHODS

Various internet data bases were searched including: PUBMED; Google; Google Scholar; EMBASE; CINAHL; Cochrane Library; PubMed Central and MEDLINE Complete. The search words that were used included: Renal biopsy; Kidney biopsy; indications for kidney biopsy, histopathology examination of kidney lesions, immunohistochemical features of renal lesions, electron microscopical features of renal lesions, special staining agents for pathological examination of kidney lesions. Twenty references were identified to write the article

4. RESULTS AND DISCUSSION

4.1 Common Indications of Medical Renal Biopsy [5]

- Unexplained acute or rapidly progressive renal failure
- Nephrotic syndrome and significant non-nephrotic proteinuria
- Persistent glomerular haematuria
- Systemic diseases with renal involvement
- Staging lupus nephritis and to classify IgA nephropathy and diabetic nephropathy
- Nephritic syndrome

4.2 Adequacy of Tissue Sampling

An adequate renal biopsy is one that contains at least 10 glomeruli on light microscopy and should have atleast one each for immunofluorescence and electron microscopy [6].

4.3 Light Microscopy (H & E Sections & Special Stains)

H and E sections along with special stains is the back bone to report renal medical biopsies.

H & E sections allow the counting of the number of glomeruli, general evaluation for ascertaining the percentage of cortex and medulla, cellular characteristics, type of inflammation and to locate the area of interest i.e., whether the disease affects the glomerulus, interstitium, vessels or tubules. Special stains commonly used are PAS, Silver methenamine, Masson's trichrome and Congo red [7,8]. The utility of the special stains is summarised in Table 1.

4.4 Immunofluorescence

Fluorescein-labelled antibodies are used to examine immunoglobulins (IgG, IgM, and IgA), complement components (C3, C1q, and C4), fibrin, and kappa and lambda light chains. They may be also used for amyloid typing, collagen IV alpha chains in hereditary nephritis, IgG subclasses [8,9].

4.5 Electron Microscopy

Electron microscopy examines glomeruli ultrastructurally and aids to concentrate on deposits, very small deposits, fibrils and changes in cellular and basement membrane structure [4].

4.6 Interpretation of Renal Biopsy

Low-power screening examination of the specimen helps in locating whether the defect is

in glomerulus, tubules, interstitium or blood vessels [9].

a) Distribution of the lesion [10,11]

It is classified as:

- Diffuse: Changes occurring in all the glomeruli.
- Focal: Changes in few glomeruli only.
- Global: Whole glomerulus is involved.
- Segmental: Only some part of glomerulus is involved.

b) Active Vs Chronic lesions [11,12].

The lesions need to be classified as either active or chronic. Table 2 summarises the examples of these lesions.

c) Abnormalities in glomerular capsule and glomerular basement membrane [12].
Table 3 summarises the common conditions and associated findings in relation to glomerular capsule while Table 4 elaborates in glomerular basement membrane.

d) Cellular proliferation [12,13].
The three common locations of cellular proliferation are: endothelial, epithelial, and mesangial cells. Abnormalities in these components with associated diseases are summarized in Table 5.

e) Vascular abnormalities [14-16].
Vascular lesions are seen in afferent and efferent arterioles and respond to injuries. Moreover, due to the high blood flow in kidneys, they are more prone to vascular injury. Table 6 shows the vascular lesions in renal biopsy.

f) Tubular abnormalities [15-17].
Tubular cells may exhibit acute reversible and irreversible damage (necrosis), intracellular accumulations, metabolic storage diseases and vacuoles. It may also show acute tubular necrosis and atrophy. Table 7 depicts the common tubular abnormalities.

g) Interstitial abnormalities [18-20].
Interstitium has lesser number of abnormalities. The common ones are edema, inflammation, and fibrosis. Edema is considered acute while fibrosis is chronic. Amyloid, immune complex deposits, and immunoglobin light chains may also be seen in interstitium.

h) Correlating H & E, IF, Special stains and EM
To arrive at a diagnosis correlating all the data is important. Table 8 summarizes all data. Photographs of H & E sections, special stains, IF and EM are provided for the common renal diseases.

4.7 Simple Format for Reporting Medical Renal Biopsies

A simple format shown below may help a renal pathologist to report renal biopsies effortlessly without causing confusion to the nephrologist. This may also aid the pathologist to focus on important components also.

Chart 1. Core (format) of renal biopsy

Glomerulus -
Number of glomeruli
Globally sclerosed:
Segmental sclerosis:
Mesangial/ endothelial/ epithelial proliferation:
Basement membrane/ capillary wall thickening:
Wire loops:
Inflammation:
Tubules –
Edema:
Inflammation:
Atrophy:
Casts:
Amyloid:
Interstitium –
Fibrosis:
Edema:
Inflammation:
Amyloid:

Vessels –
Hypertrophy:
Hyaline or hyperplastic arteriosclerosis:
Amyloid:

Special stains –
PAS:
Silver:
Congo red:
Masson Trichrome:
Immunohistochemistry –
IgG:
IgA:
C3:
Diagnosis:

Table 1. Utility of the special stains

Special stains	Utility
PAS	Glomerular basement membrane, mesangium, tubular basement membrane, hyaline – pink to red
Silver methenamine	Basement membrane details – stains black
Masson's trichrome	Extracellular glomerular matrix and tubular basement membrane – blue or green
Congo red	Amyloid

Table 2. Examples of active and chronic lesions

Active lesions	Chronic lesions
Necrosis	Fibrous crescents
Edema	Tubular atrophy
Cellular casts	Interstitial fibrosis
Active inflammation	Vascular sclerosis

Table 3. Abnormalities in glomerular capsule

	Common conditions	Associated findings
Capsular basement membrane thickening	Diabetes mellitus	Capsular drop
Capsular space obliteration	Glomerulonephritis Crescents or necrosis	

Table 4. Abnormalities in glomerular basement membrane

	Common conditions	Associated findings
1.Thick GBM		
a. Negative IF		
	Diabetic nephropathy	EM – Lamina densa thick No splitting by silver stain
	Hereditary nephritis	Silver stain irregular EM – Basket weaving
b. Positive IF		
	Membranous nephropathy	Spikes by silver stain Subepithelial deposits - EM
	Membranoproliferative glomerulonephritis	Silver stain – GBM splitting Subendothelial deposits - EM

	Common conditions	Associated findings
	Amyloid	Positive light chains depending upon type of amyloid
	Fibrillary glomerulonephritis	Variable splitting by silver Fibrils in EM
2. Thick GBM		
	Alport's syndrome	Silver stain irregular EM – Basket weaving
	Benign familial haematuria	Thin GBM - EM

GBM: Glomerular basement membrane, EM: Electron microscopy, IF: Immunofluorescence

Table 5. Abnormalities in glomerular components

	Common conditions	Associated findings
1. Epithelial	**Crescentic GN**	
Linear GBM deposition	Anti-GBM disease	Positive anti-IgG linear staining along GBM
Immune complex	IgA nephropathy	Positive immune deposits in mesangium
	Post-infectious GN	Positive immune deposits along capillary walls
	Lupus	Full-house pattern of staining in mesangium and long capillary walls, tubuloreticular inclusions on EM
Pauci-immune	Granulomatosis with polyangiitis Microscopic angiitis	No deposits on IF No deposits on IF
2. Mesangial		
With nodule formation	Light chain deposition disease	Linear staining for light chains along GBM & TBM, granular deposits along GBM & TBM on EM
	Membranoproliferative GN	Double contours with subendothelial deposits, cellular elements and new basement membrane formation
	Diabetic nephropathy	PAS and silver positive nodules with negative IF Thick GBM & TBM
	Amyloidosis	PAS & silver negative nodules with positive IF staining for or light chains in AL amyloidosis
Without nodule formation	Post-infectious GN	Positive granular IgG & C3 along capillary walls; Subepithelial humps and subendothelial deposits in EM
	Ig A nephropathy	IgA deposits in mesangium
	C3 glomerulopathy	C3 in mesangium and along capillary walls on IF, and the absence of IgG
3. Endothelial	Post-infectious GN	Positive granular IgG & C3 along capillary walls; Subepithelial humps and subendothelial deposits in EM
	Membranoproliferative GMN	Positive granular IgG, IgM, C1q, C3 or light chains depending on

	Common conditions	Associated findings
	SLE	cause, double contours on EM Full house staining on IF microscopy; mesangial, subepithelial, or subendothelial deposits depending on class of SLE

GN: Glomerulonephritis, TBM:Tubular basement memebrane, SLE: Systemic lupus nephritis, GBM: Glomerular basement membrane

Table 6. Common vascular lesions in renal pathology

	Common conditions	Associated findings
Sclerosis	Hypertension	Ischemic glomeruli with thickening of the glomerular basement membranes and wrinkling of the capillary loops
Thrombosis	HUS/TTP Malignant hypertension	Thrombi in glomerular capillaries, arterioles Onion skinning of the vessel walls with hypertrophy of the media
Fibrinoid necrosis	Malignant hypertension Polyarteritis nodosa HUS/TTP	Onion skinning of the vessel walls with hypertrophy of the media Arteritis, with fibrinoid necrosis and inflammation of vessel walls Thrombi in glomerular capillaries, arterioles
Vasculitis	Vasculitis	Depends on type. e.g., in granulomatosis with polyangiitis, granulomatous inflammation
Emboli	Atheroembolism	Cholesterol atheroemboli in glomerular capillaries and arteries
Hyalinosis - Eccentric	Hypertension Diabetes	Ischemic glomeruli with thickening of the glomerular basement membranes and wrinkling of the capillary loops Diffuse and nodular glomerulosclerosis

HUS: Hemolytic uremic syndrome, TTP: Thrombotic thrombocytopenic purpura

Table 7. Common tubular abnormalities

Lesions	Common conditions	Associated findings
1.Necrosis	Ischemic and toxic ATN	Flattened tubular epithelial cells, mitotic figures
2. Edema	Ischemic and toxic ATN, thrombosis	Associated with interstitial inflammation; but no inflammation in renal vein thrombosis
3. Inflammation		
a. Polymorph	Rein vein thrombosis	Increased neutrophils in glomerular capillaries
b. Lymphocyte	Acute interstitial nephritis Hypersensitivity reaction	Tubulitis Eosinophil infiltrate
c. Eosinophil	Churg- Strauss vasculitis	Eosinophil infiltrate
4. Granuloma		
a. Necrotising	Tuberculosis & fungal	Positive AFB stains in TB
b. Confluent	Sarcoidosis	Perivascular granulomas
5. Intratubular material - Pigmented cast	Myoglobin in rhabdomyolysis	Positive immunohistochemistry for myoglobin
6. Atrophy		

Lesions	Common conditions	Associated findings
a. Focal	Glomerular ischemia	Distended Bowman's capsule,
b. Diffuse	Advanced renal disease	with thickening and wrinkling of
c. Disproportionate		glomerular capillaries
	Renal artery stenosis & renal vein thrombosis	Focal global glomerulosclerosis
	Obstructive uropathy	Tamm-Horsfall protein in tubules
7. Fibrosis - Patchy	Chronic pyelonephritis	PAS-positive hyaline casts
8. Dilatation	Obstructive uropathy	Tamm-Horsfall protein in tubules

ATN: Acute tubular necrosis, AFB: Acid fast stain, TB: Tuberculosis

Table 8. Correlating H & E, Special stains, IF & EM of common renal diseases

Disease	H & E	Special stains	IF	EM
Minimal change disease	Normal appearing components	Normal appearing	No deposits	Effacement of foot processes
Membranous nephropathy	Thickened capillary walls	Silver: Thickened capillary walls and spikes	Fine granular staining for IgG and C3 in capillary walls	Subepithelial deposits
Post-streptococcal glomerulonephritis	Hypercellular glomeruli, abundant neutrophils	Thickened basement membrane	Coarse granular staining for IgG and C3 in capillary walls	Large subepithelial deposits
Rapidly progressive glomerulonephritis – Pauci-immune	Crescents	Active and chronic crescents	No deposits	No deposits
IgA nephropathy	Mesangial proliferation	Mesangial proliferation	IgA deposits in mesangial area	Deposits in mesangial and para-mesangial area
Diabetic nephropathy	Nodular eosinophilic deposits	Nodular eosinophilic deposits	No deposits	No deposits, thickened basement membrane
Membranoproliferative glomerulonephritis	Mesangial and endocapillary proliferation	Silver: Double contours	Coarse granular staining for IgG and C3 in capillary walls	Subendothelial deposits
Dense deposit disease	Mesangial and endocapillary proliferation	Silver: Double contours	Coarse granular staining for C3 in capillary walls	Ribbon like intra-membranous deposits
Amyloidosis	Nodular eosinophilic deposits	Congo red: Nodular eosinophilic	AL type: deposits seen	Fibrils of 10 - 12nm

Disease	H & E	Special stains	IF	EM
		deposits		
Lupus nephritis	Mesangial proliferation, wire loops	Mesangial proliferation	Full house positivity	Subendothelial and mesangial deposits

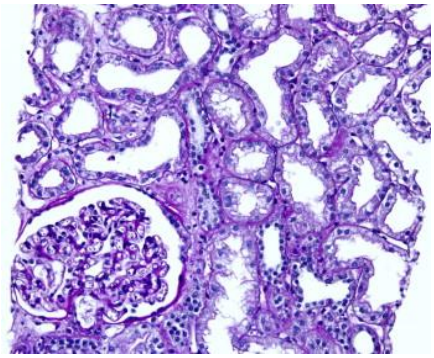

Fig. 1a. H & E - Preserved cortex normal-appearing glomerulus

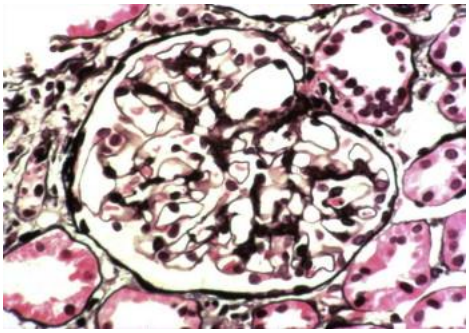

Fig. 1b. Silver stain - The glomerulus shows no proliferation, sclerosis, inflammation, or necrosis and Bowman space is unremarkable

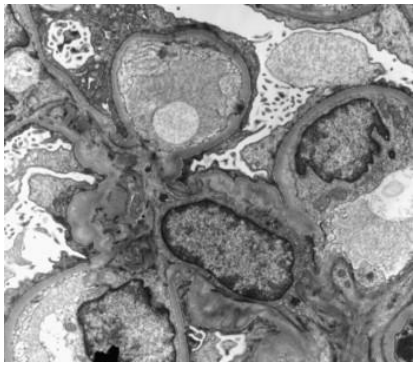

Fig. 1c. EM - Diffuse effacement of foot processes of podocytes

Fig. 1. Minimal change disease (Source: AJKD)

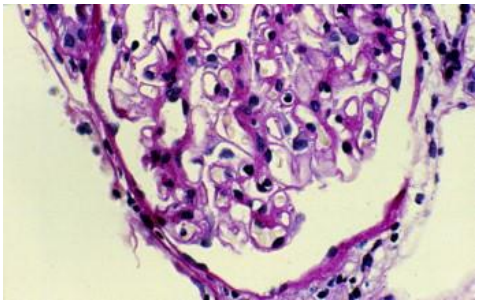

Fig. 2a. H & E – Thickened capillary walls

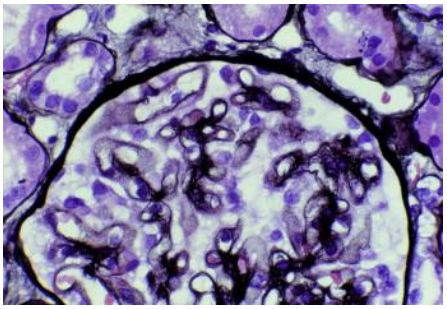

Fig. 2b. Silver stain – Thickened capillary walls and spikes

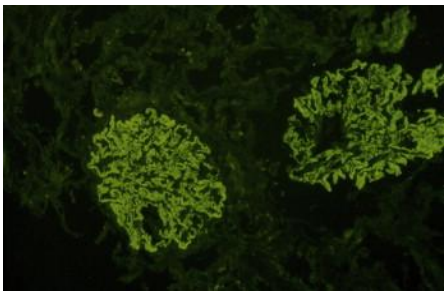

Fig. 2c. IF - Diffuse granular capillary wall IgG

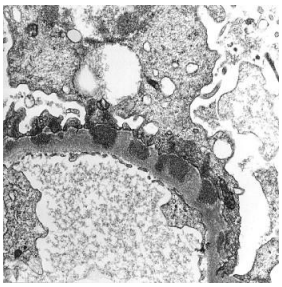

Fig. 2d. EM – Subepithelial deposits

Fig. 2. Membranous nephropathy
(Source: AJKD)

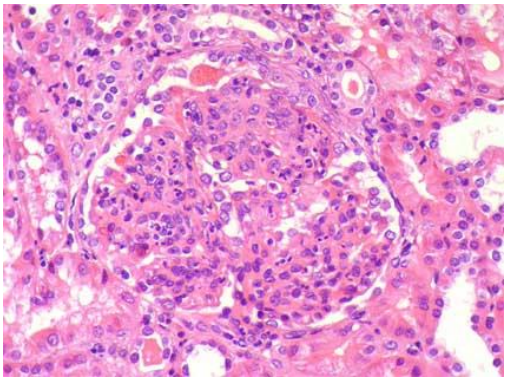

Fig. 3a. H & E - Hypercellular glomeruli and abundant neutrophils

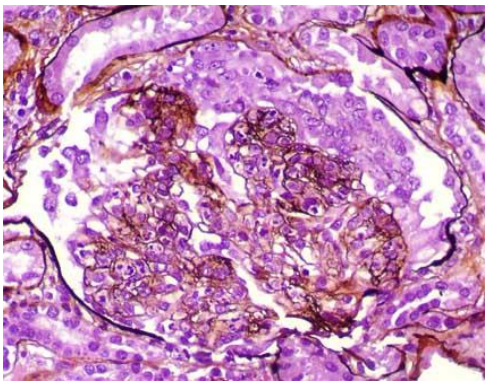

Fig. 3b. Silver - Hypercellular glomeruli and abundant neutrophils

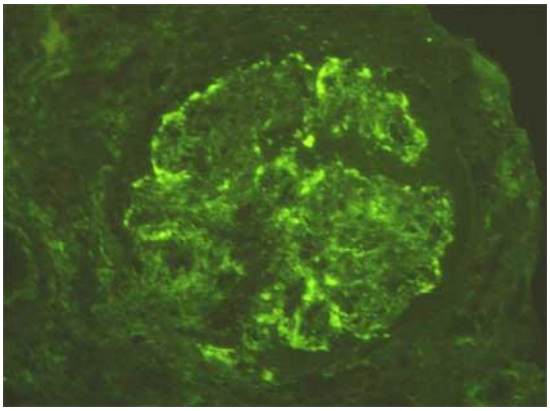

Fig. 3c. IF – Coarse granular staining of IgG in capillary walls

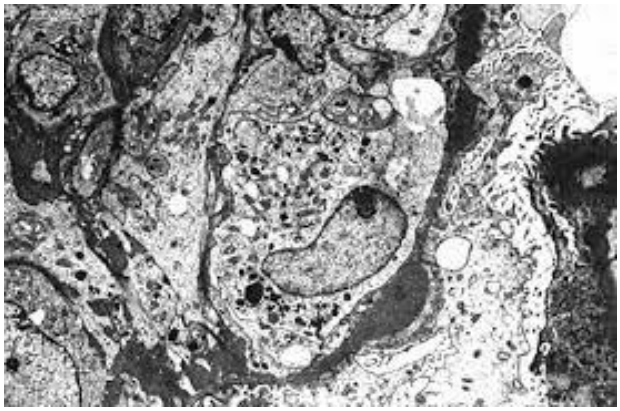

Fig. 3d. EM – Large subepithelial deposits

Fig. 3. Post-streptococcal glomerulonephritis
(Source: Kidney pathology)

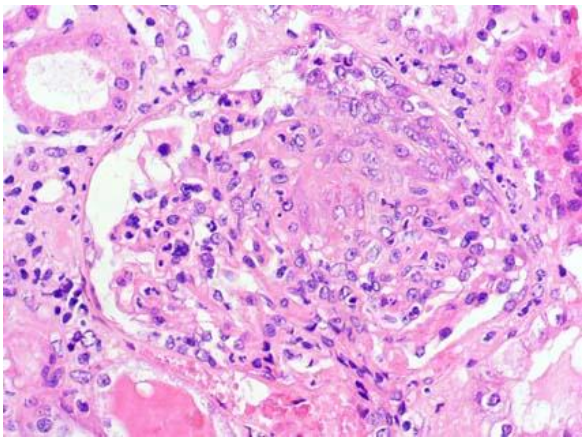

Fig. 4a. H & E: Necrotic debris & crescents

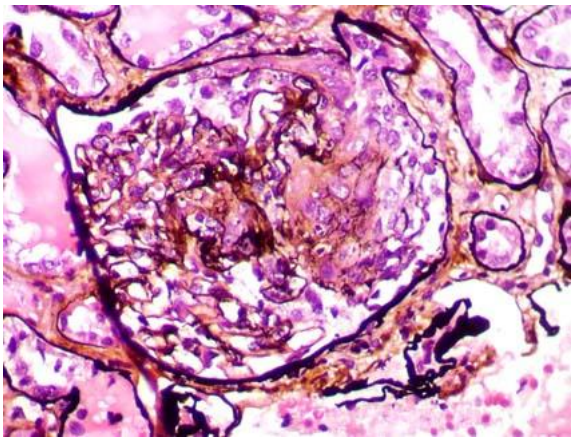

Fig. 4b. Silver: Crescents

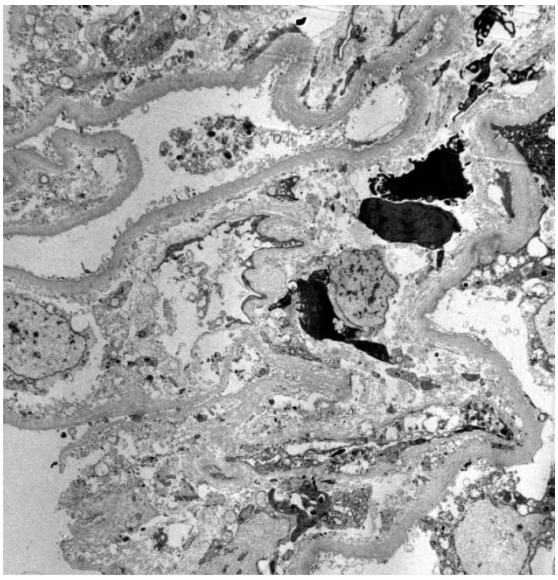

Fig. 4c. EM: No deposits

Fig. 4. Rapidly progressive glomerulonephritis – Pauci-immune
(Source: Kidney pathology)

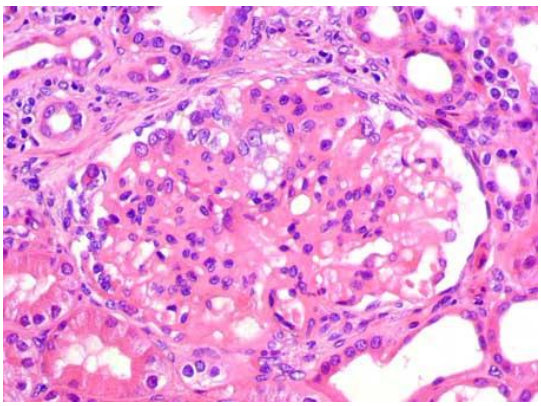

Fig. 5a. H & E - Mesangial proliferation

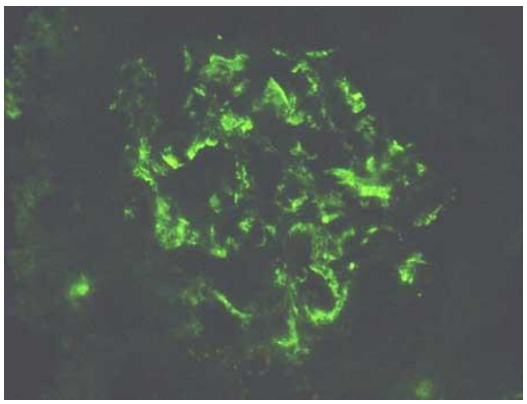

Fig. 5b. IF - Mesangial IgA deposits

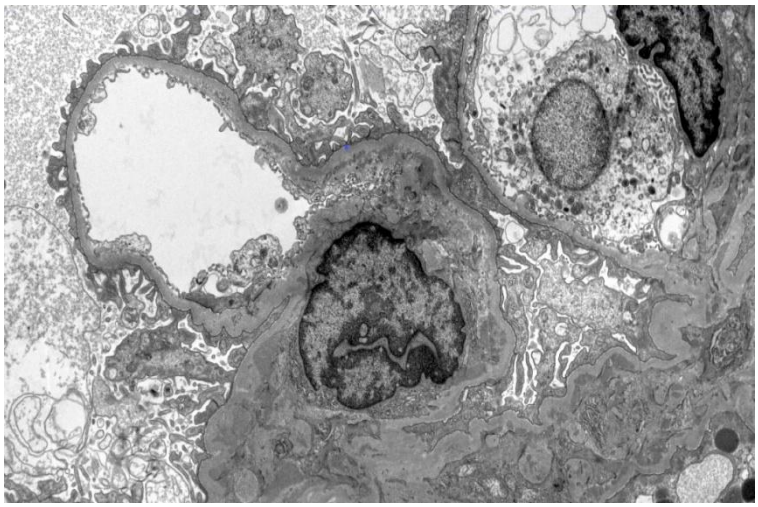

Fig. 5c. EM - Mesangial and para-mesangial deposits

Fig. 5. IgA nephropathy
(Source: Kidney pathology)

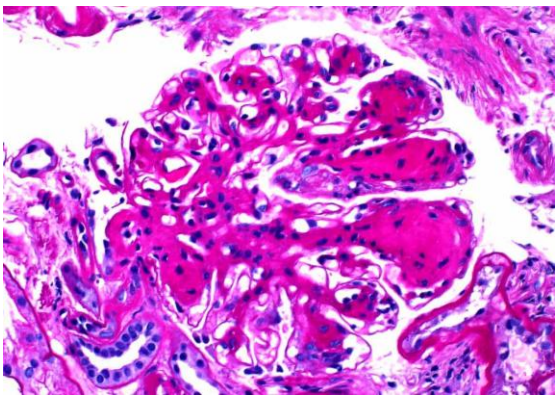

Fig. 6a. H & E - Nodular deposits

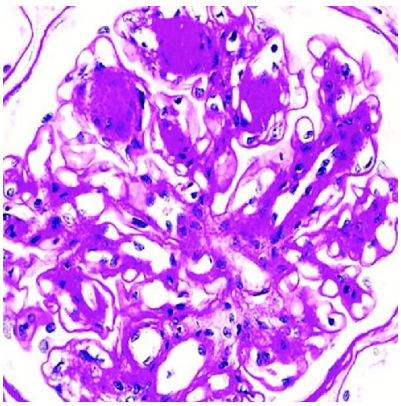

Fig. 6b. PAS – Nodular deposits

Fig. 6. Diabetic nephropathy
(Source: Kidney pathology)

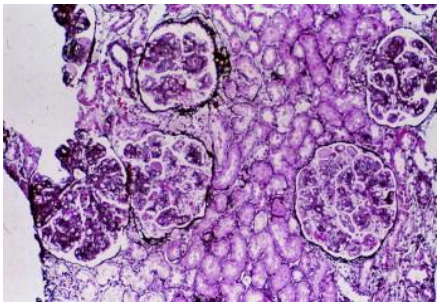

Fig. 7a. Silver – Mesangio-capillary

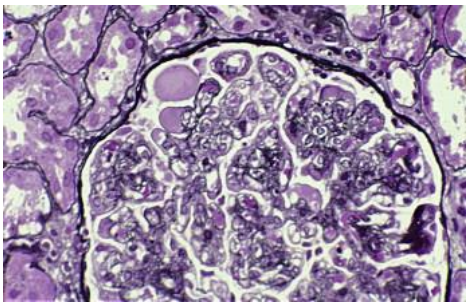

Fig. 7b. Silver – Double contours proliferation

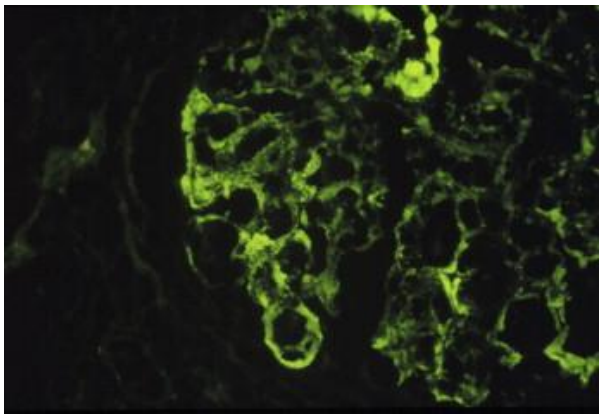

Fig. 7c. IF – IgG Coarse granular staining

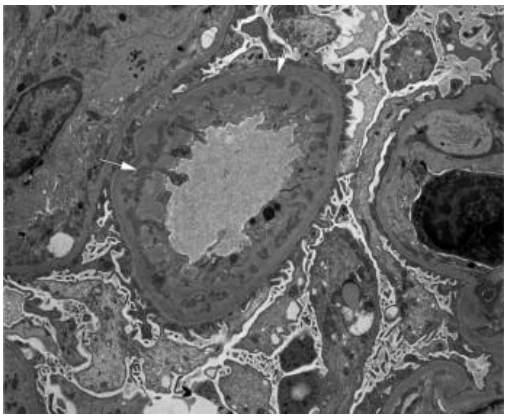

Fig. 7d. EM – Subendothelial deposits

Fig. 7. Membranoproliferative glomerulonephritis
(Source: AJKD)

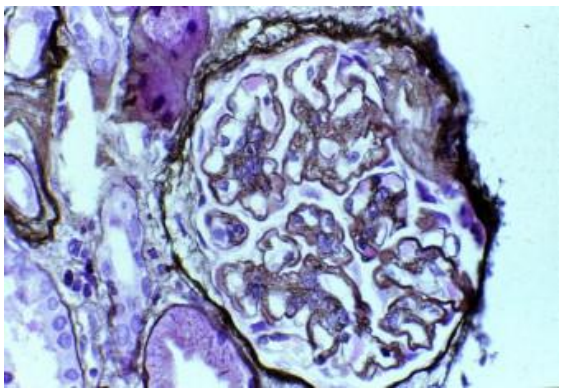

Fig. 8a. Silver - Double contours

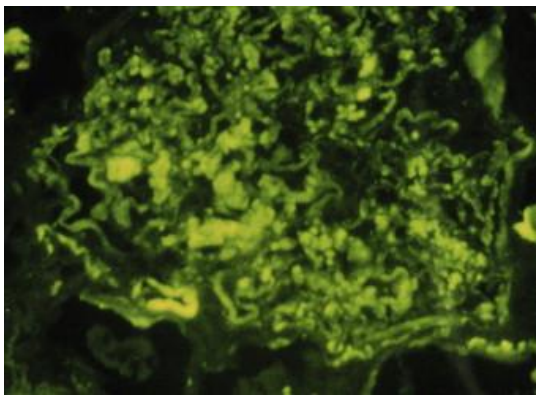

Fig. 8b. IF – Globular C3 deposits in capillary walls

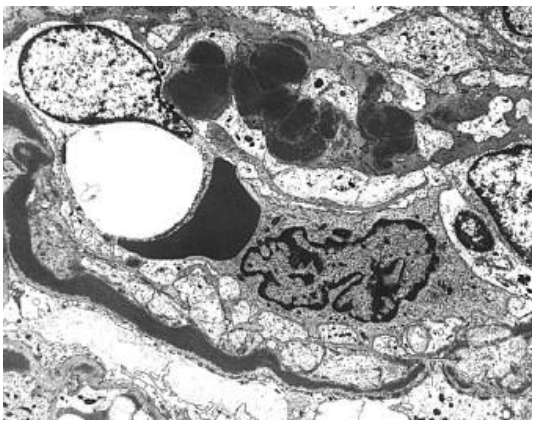

Fig. 8c. EM – Ribbon like intramembranous deposits

Fig. 8. Dense deposit disease
(Source: AJKD)

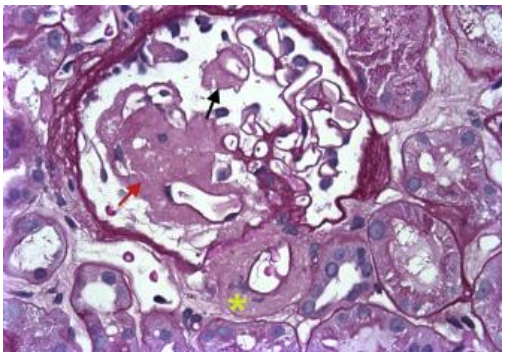

Fig. 9a. PAS - acellular, pale, eosinophilic

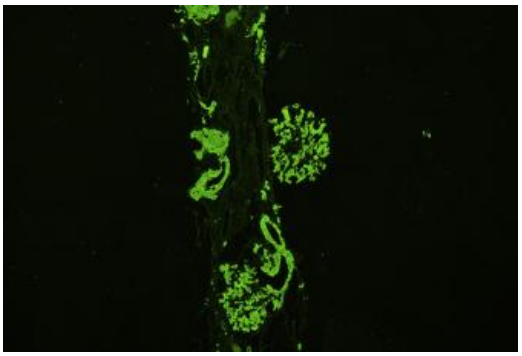

Fig. 9b. IF- AL amyloidosis with λ light chain–restricted staining in glomeruli

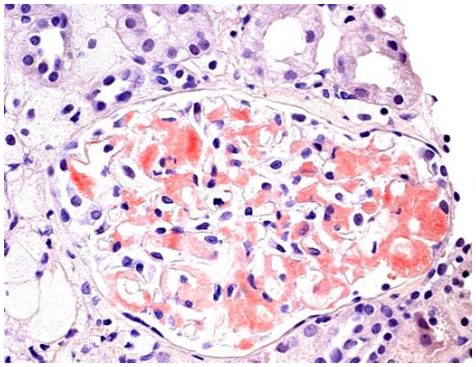

Fig. 9c. Congo red - congophilic staining within the glomerulus

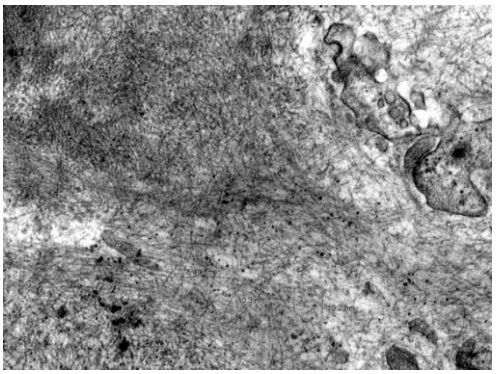

Fig. 9d. EM - Randomly arranged non-branching fibrils with a diameter of 10-12 nm

Fig. 9. Amyloidosis
(Source: AJKD)

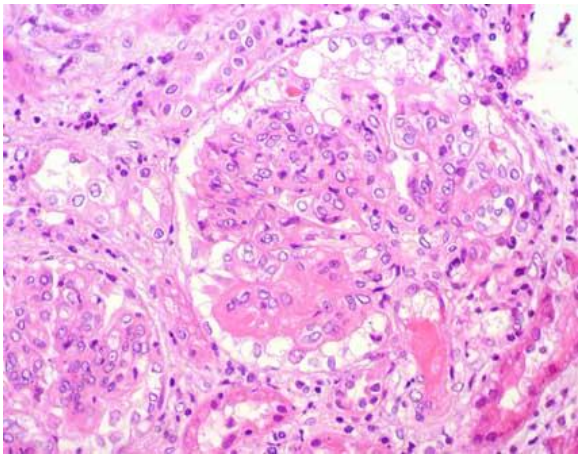

Fig. 10a. H & E – Hyaline thrombi, fibrosis, hypercellularity

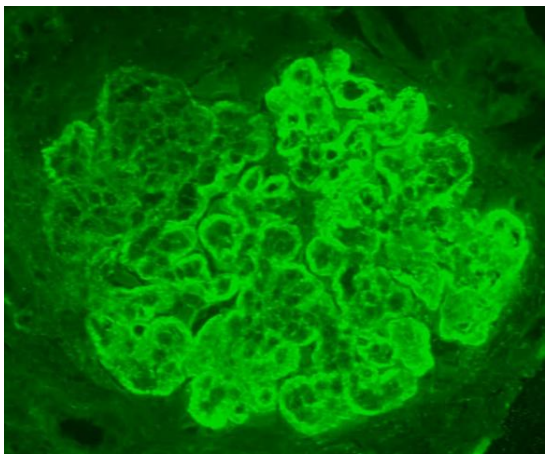

Fig. 10b. IF – IgG staining granular capillary wall, subepithelial and mesangium

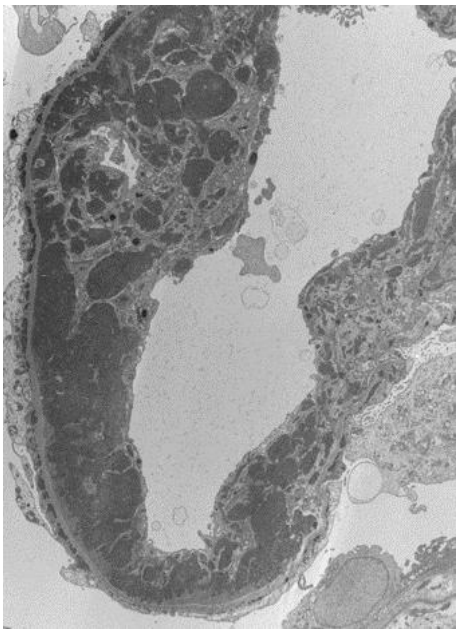

Fig. 10c. EM – Subendothelial, intramembranous and subepithelial deposits

Fig. 10. Lupus nephritis

(Source: Kidney pathology)

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5. CONCLUSION

Renal biopsy is a vital tool for the understanding of the pathology of various renal diseases. It helps in evidence-based medicine and proper patient care. Both pathologists and nephrologists should work together for proper clinico-pathological correlation. H & E, special stains, IF, and EM together must be done routinely in all renal biopsies. If properly interpreted, renal biopsies are a great source for appropriate therapeutic strategy as well as to provide key prognostic information.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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