

Review

Tubulointerstitial nephritis in systemic lupus erythematosus: innocent bystander or ominous presage

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Summary. SLE-associated tubulointerstitial injury (SLE TIN) is increasingly recognized in two forms, i.e., *secondary* and *primary*. The secondary form coexists with lupus glomerulonephritis, whereas the primary form develops against the background of no or mild glomerular or vascular involvement.

Secondary SLE TIN is frequent, but its frequency and severity correlate with the class of the associated lupus glomerulonephritis (GN), being almost universal in Class IV lupus GN and less frequent in GN of other classes. Although the presence of underlying GN may mask its clinical manifestation, secondary SLE TIN has a major prognostic implication for the renal outcome. Yet, SLE TIN is not factored in the current therapy-focused International Society of Nephrology/Renal Pathology Society schema of renal lupus classification, and its management remains to be elucidated. The pathogenesis of secondary SLE TIN is either immunologic, i.e., the tubulointerstitial injury being mediated by SLE-related immunologic mechanisms akin to those responsible for lupus GN; or non-immunologic, i.e., a nonspecific tubulointerstitial injury secondary to any type of advanced glomerular lesion, regardless of etiology.

Primary SLE TIN is rare with about 15 reported cases. It has a rather uniform and distinctive clinical manifestation including acute kidney injury with no or mild proteinuria. It responds well to steroid and usually carries a good prognosis. Its pathogenesis is almost

certain immunologic, with immunoglobulin/complement deposits along the tubular basement membrane in each reported case.

In spite of these profound clinical implications, the current review underlies a limited knowledge on the pathobiology of SLE TIN.

Key words: Systemic lupus erythematosus, Primary lupus tubulointerstitial nephritis, Secondary lupus tubulointerstitial nephritis, Lupus glomerulonephritis, Mechanism, Prognosis, Treatment

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune chronic inflammatory disease that affects multiple organ systems. The disease shows a strong female predominance with a male:female ratio of 1:10 and classically occurs in women of childbearing age (Seshan and Jennette, 2009). The renal involvement in SLE, referred to as “lupus nephritis”, is a dreaded complication because it is associated with significant morbidity and mortality. The frequency of lupus nephritis in SLE patients ranges from 27-70%. Asians have a higher predisposition to develop lupus nephritis as compared to Europeans or Americans (Wang et al., 1997; Cervera et al., 2009). The prevalence of lupus nephritis in the US population ranges from 14 to 50 per 100,000 people (Alarcon et al., 2002; D’Agati, 2007).

Although the glomerular, tubulointerstitial, or vascular compartment can be independently affected in the spectrum of SLE-associated renal injury,

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glomerulonephritis (GN) is the most common form of lupus nephritis. A classification scheme jointly proposed by the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) classifies lupus GN into six categories: Minimal mesangial lupus GN (Class I); mesangial proliferative lupus GN (Class II); focal lupus GN (Class III); diffuse lupus GN (Class IV); membranous lupus GN (Class V); and advanced sclerotic lupus GN (Class VI) (Weening et al., 2004). This classification scheme provides guidelines for treatment and is based entirely on renal biopsy evaluation of *glomerular* changes. Tubulointerstitial or vascular lesions are not a part of this classification scheme (D'Agati, 2007).

SLE-associated tubulointerstitial injury (SLE TIN) is increasingly recognized in two forms, i.e. *secondary* and *primary*. In most cases, SLE TIN is found *in association* with lupus GN. This type of lesion, termed *secondary* SLE TIN, displays a variable frequency and severity depending on the class of the associated lupus GN, and pathogenetically may be of either immunologic or non-immunologic mechanism. The former implies that the tubulointerstitial injury is mediated by SLE-related immunologic mechanisms akin to those responsible for lupus GN. The latter, in contrast, reflects a nonspecific type of tubulointerstitial injury secondary to any type of advanced glomerular lesion, regardless of etiology. SLE TIN may also develop *without* glomerular or vascular involvement. This type of tubulointerstitial injury, termed *primary* SLE TIN, is rare and is pathogenetically due to *selective* SLE involvement of the tubulointerstitial compartment.

Awareness of SLE TIN is important for both clinical and biologic connotations. Predictors of progression of renal disease in SLE patients traditionally include gender, serum creatinine, serologic findings, and the lupus GN class. However, the tubulointerstitial lesions are also clinically significant, since they are not only frequent in SLE patients, but may also portend independent prognostic/therapeutic implications (Howie et al., 2003; Yu et al., 2010; Hsieh et al., 2011). Furthermore, recent experimental and clinical evidences suggest that the pathogenesis of SLE TIN, even in the cases of immunologic etiology, may be different from that of the associated lupus GN (Satoskar et al., 2011).

In spite of its high frequency, potential clinical significance, and unique pathogenesis, the literature on SLE TIN is quite limited, in contrast to a voluminous output on lupus GN. This review consolidates the published literature on SLE TIN to provide an integrated review of the clinicopathologic attributes and pathogenesis of this entity.

Secondary SLE TIN

Clinical presentation

A definitive diagnosis of SLE requires the presence of at least 4 of 11 sequential or simultaneous findings

recommended by the American Rheumatological Association (Seshan and Jennette, 2009). They include skin manifestations, oral ulcer, arthritis, serositis, renal disease, neuropsychiatric disease, hematologic abnormalities, thrombocytopenia and positive serologic findings such as anti-nuclear antibodies, anti-DNA antibodies, anti-smith antibodies and anti-phospholipid antibodies (Tan et al., 1982; Hochberg, 1997). The renal manifestations in SLE patients encompass the entire spectrum of renal abnormalities such as proteinuria, asymptomatic hematuria, nephrotic syndrome, nephritic syndrome, hypertension, renal failure, and active urine sediment. These manifestations, however, usually reflect the glomerular involvement (lupus GN).

Renal biopsy studies clearly show that the frequency and severity of SLE TIN vary depending on the class of the associated lupus GN. It is most severe and common (96%) in diffuse lupus GN (Class IV), and less so in focal (Class III) lupus GN (61%) or mesangial proliferative (Class II) lupus GN (45%). It can also be seen in lupus membranous (Class V) GN (62%), but is perhaps not present in minimal mesangial (Class I) lupus GN (D'Agati, 2007; Yu et al., 2010). It is emphasized that tubulointerstitial changes may be inconspicuous or rarely absent, even in the background of severe and active GN. This discrepancy lends further evidence to potentially independent pathogenesis for the glomerular and tubulointerstitial involvement in lupus nephritis.

Against the background of protean and often pronounced clinical manifestations of lupus GN, the frequently associated SLE TIN does not seem to manifest a specific clinical presentation and, in general, does not seem to modify in a specific way the clinical manifestations of the underlying lupus GN. Kozeny et al. (1987) found no correlation between tubular dysfunction and the severity of the interstitial lesions in renal biopsies. Similarly, Schwartz et al. (1982) found no correlation between renal dysfunction and extra-glomerular immune deposits. However, the clinical relevance of SLE TIN has also been observed. O'Dell et al. (1985) suggested that SLE TIN is associated with higher serum creatinine at biopsy and at follow-up. Hill et al (2001) found that proteinuria may correlate with tubulointerstitial lesions on light microscopy (LM) but not with tubulointerstitial deposits by immunofluorescence (IF). The same study showed that attenuation of proteinuria reduced the tubulointerstitial lesions. Tubular dysfunction including renal tubular acidosis was rarely reported, but probably represents an under-recognized clinical presentation of SLE TIN (Fang and Chen, 2000; Li et al., 2005). Early recognition and treatment of this condition was shown to prevent progression to acute renal failure.

Morphologic findings

SLE TIN features lesions involving the renal tubules and interstitium, against a background of lupus GN. Although the histologic spectrum of the tubulointerstitial

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changes is the same, the frequency and severity of these changes vary with the class of the associated lupus GN (Fig 1A-D).

Light microscopy (LM)

The tubulointerstitial changes are active or chronic, but often display both components.

Active tubulointerstitial changes include tubulitis (intraepithelial lymphocytes), tubular epithelial cell degenerative and regenerative changes, and apoptosis (Fig. 2A,B). The damaged tubules may show granular/cellular casts, macrophages, or fat bodies. Another type of active tubular changes, which may reflect prolonged and heavy proteinuria itself, rather than an inflammatory process, includes cytoplasmic vacuolization reflecting accumulation of lipid and

protein reabsorption droplets, involving predominantly proximal convoluted tubules (Fig. 2A). These tubular changes are seen in conjunction with active interstitial changes including inflammation and edema. The interstitial inflammation is often diffuse and composed predominantly mononuclear cells such as lymphocytes, monocytes and plasma cells (Fig. 2B). Neutrophils and eosinophils are rarely seen. Peritubular capillaritis is rarely seen (Fig. 2A). Chronic changes include interstitial fibrosis surrounding atrophic tubules, and thickened peritubular capillaries (Fig. 2C,D), and accumulation of interstitial foam cells, perhaps secondary to long-standing nephrotic range proteinuria. Active lesions may be patchy or diffuse and may occur in conjunction with chronic lesions. It is emphasized that these LM changes, even when severe, fall into to the spectrum of tubulointerstitial nephritis of diverse causes

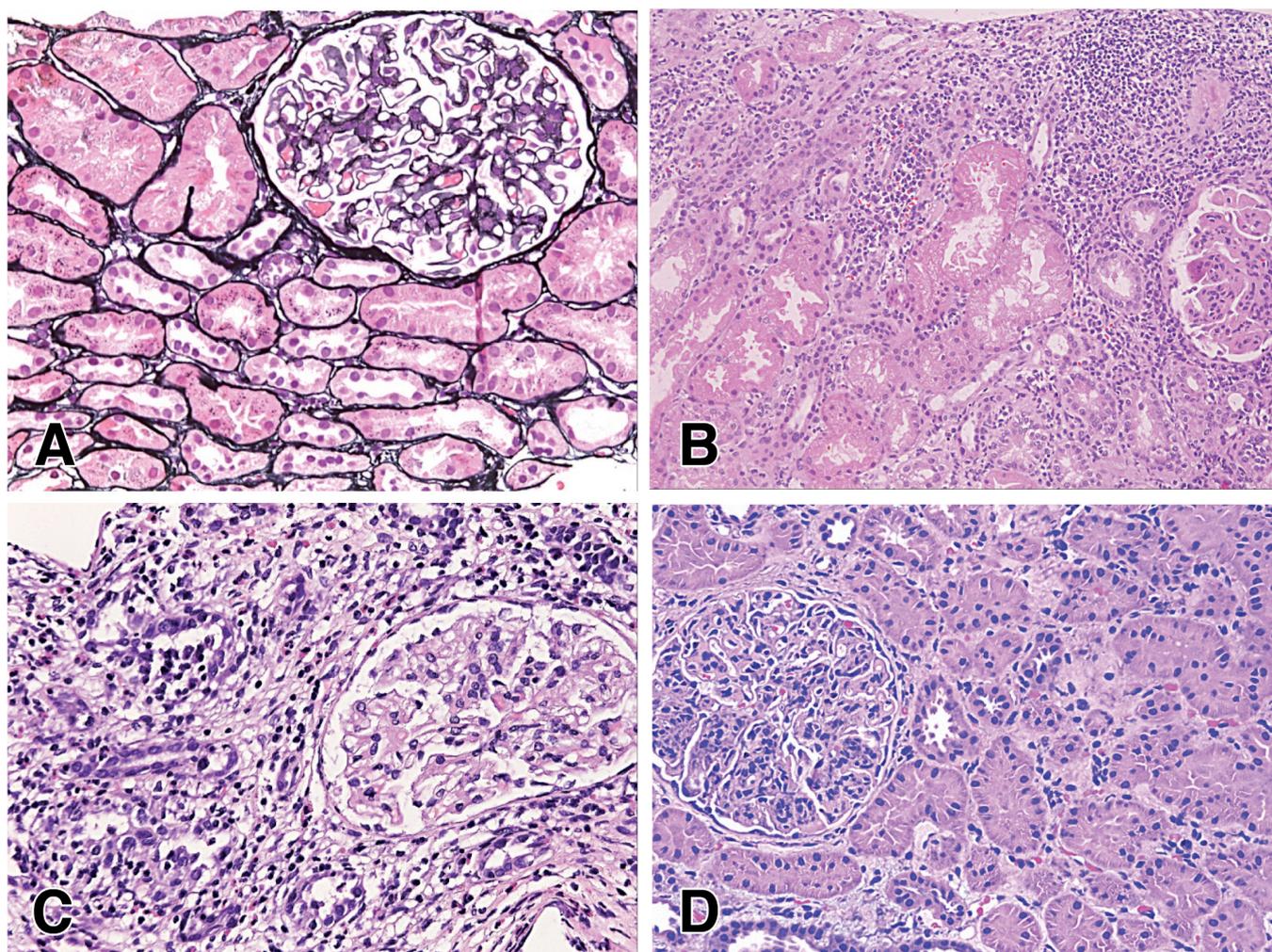


Fig. 1. Lupus tubulointerstitial nephritis (TIN) in relation to lupus glomerulonephritis (GN). **A.** Virtually no tubulointerstitial changes in mesangial (Class II) lupus GN (Jones' silver stain). **B.** Marked acute TIN in diffuse proliferative (Class IV) lupus GN (H&E stain). **C.** Marked acute TIN in membranous (Class V) lupus GN (H&E stain). **D.** Minimal TIN in diffuse proliferative (Class IV) lupus GN (H&E stain). x 200

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and are not specific for lupus involvement. Furthermore, these changes are not significantly different for the biopsies with or without tubulointerstitial deposits of immunoglobulins/complement components.

Active tubulointerstitial lesions are more frequent in Class IV lupus GN, than in Class III or Class II lupus GN. Chronic tubulointerstitial lesions are seen more commonly in class V (membranous) GN or mixed proliferative or membranous lupus GN (O'Dell et al., 1985; D'Agati, 2007). Yu et al. (2010) reported that active tubulointerstitial lesions and the severity of interstitial inflammation correlate with features of glomerular activity such as cellular crescents,

karyorrhexis/fibrinoid necrosis and subendothelial hyaline deposits. Similarly, chronicity features such tubular atrophy and interstitial fibrosis correlate with glomerular features of chronicity such as glomerulosclerosis and fibrous crescents. This explains the variability in severity of tubulointerstitial lesions in different classes of lupus GN.

Immunofluorescence (IF)

Immunoglobulins and/or complement components are noted along the tubular basement membrane in 33-50% of renal biopsies with lupus GN, all of which also

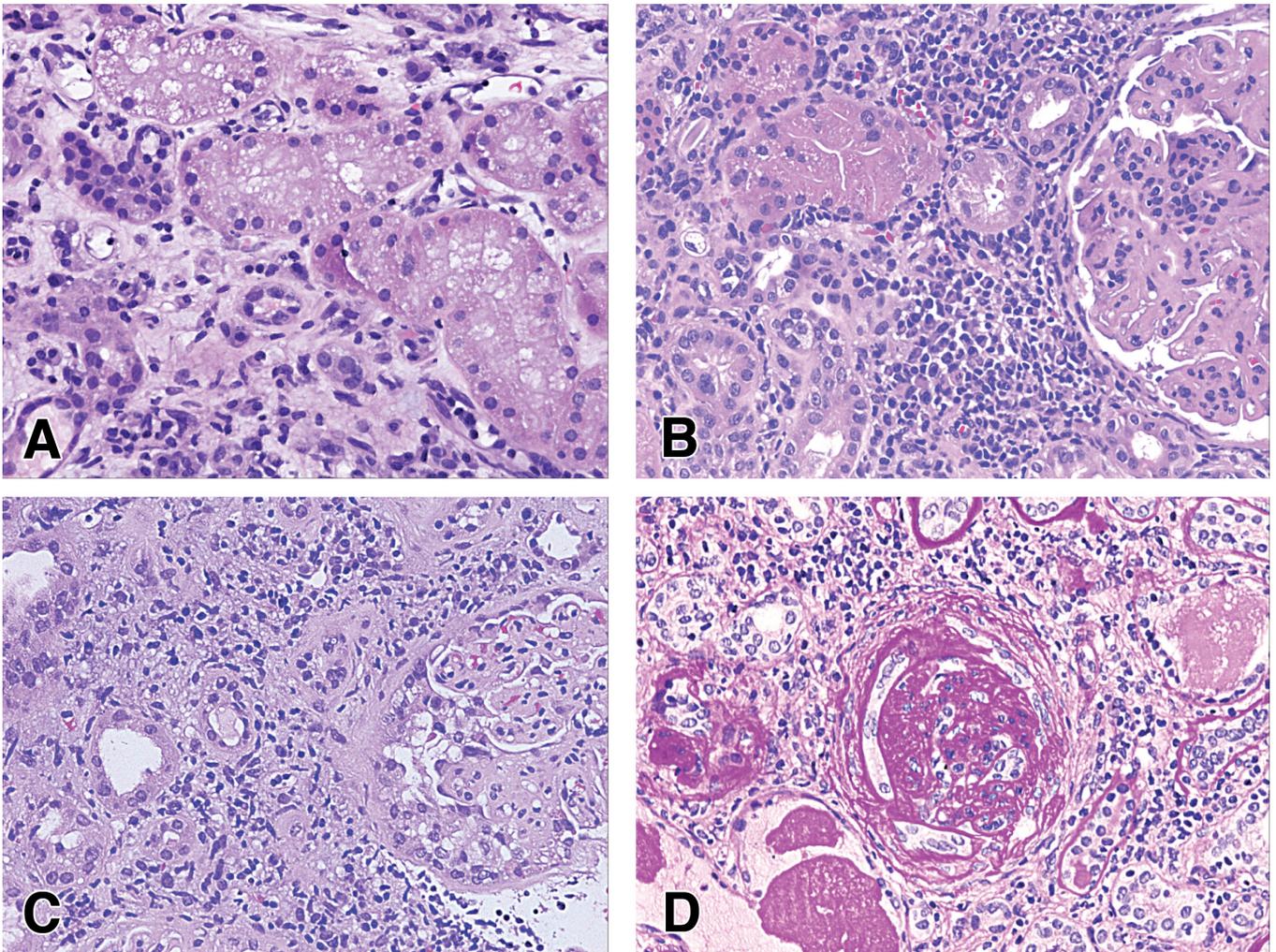


Fig. 2. Active and chronic changes in lupus tubulointerstitial nephritis **A.** The tubular cells show cytoplasmic vacuolization (upper right), which may be related to heavy proteinuria secondary to the associated glomerulonephritis (GN). There are also tubulitis (left lower corner) and peritubular capillaritis (right lower corner), tubular atrophy, interstitial mononuclear inflammatory cell infiltrate, interstitial edema, and early fibrosis (H&E stain). **B.** Marked mononuclear inflammatory cell infiltrates, forming aggregates with mild focal tubular atrophy and interstitial fibrosis, seen in association with a glomerulus with Class IV changes including cell proliferation and abundant capillary deposits of material that is electron dense deposits by electron microscopy (H&E stain). **C.** Chronic changes including tubular atrophy, tubular dilatation, interstitial fibrosis, and interstitial inflammation, associated with class IV lupus GN (H&E stain). **D.** Marked chronic tubulointerstitial changes, including tubular hyaline casts, associated with advanced sclerosing (Class VI) lupus GN (PAS stain). x 200

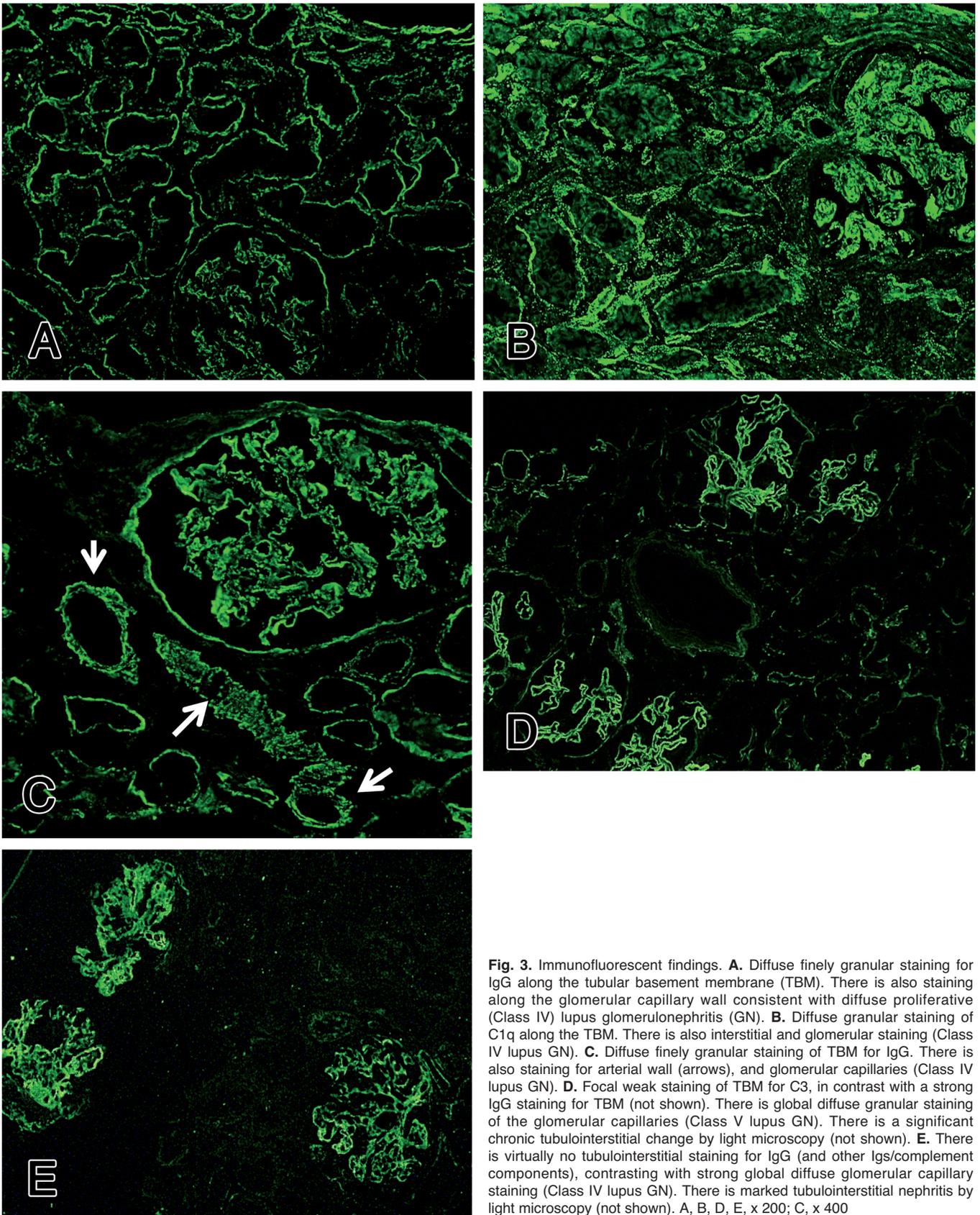


Fig. 3. Immunofluorescent findings. **A.** Diffuse finely granular staining for IgG along the tubular basement membrane (TBM). There is also staining along the glomerular capillary wall consistent with diffuse proliferative (Class IV) lupus glomerulonephritis (GN). **B.** Diffuse granular staining of C1q along the TBM. There is also interstitial and glomerular staining (Class IV lupus GN). **C.** Diffuse finely granular staining of TBM for IgG. There is also staining for arterial wall (arrows), and glomerular capillaries (Class IV lupus GN). **D.** Focal weak staining of TBM for C3, in contrast with a strong IgG staining for TBM (not shown). There is global diffuse granular staining of the glomerular capillaries (Class V lupus GN). There is a significant chronic tubulointerstitial change by light microscopy (not shown). **E.** There is virtually no tubulointerstitial staining for IgG (and other Igs/complement components), contrasting with strong global diffuse glomerular capillary staining (Class IV lupus GN). There is marked tubulointerstitial nephritis by light microscopy (not shown). A, B, D, E, x 200; C, x 400

display LM features of SLE TIN, albeit of variable severity (Schwartz et al., 1982; O' Dell et al., 1985; Park et al., 1986) (Figs 3A-E). In a few of these cases there is also peritubular capillary or interstitial deposits. It is emphasized that these deposits are not seen in up to 50% of cases with light microscopic features of SLE TIN, in keeping with a possible non-immunologic mechanism of the tubulointerstitial injury in these cases (Fig 3E). These deposits are more frequently seen with diffuse (Class IV) lupus GN (Fig. 3A,B), but may also be seen with lupus GN of other classes (Park et al., 1986). The tubular basement membrane deposits are commonly granular and discrete, and can involve any or all segments of the nephron to a variable extent, ranging from very focal to diffuse (Schwartz et al., 1982) (Fig. 3A,B). Linear tubular basement membrane deposition has not been reported. About half of cases show tubular epithelial cell nuclear staining for immunoglobulins, almost always IgG, but not complement components. Vascular deposits occur in peritubular capillaries; however, these deposits can be seen in intima and media of small and large blood vessels (Fig. 3C) (Schwartz et al., 1982; Park et al., 1986). Interstitial deposits are rarely seen and are associated with TBM deposits (Fig 3B).

The composition of the deposits is variable. Among immunoglobulins, IgG is the most common and may be the only immunoglobulin present. IgA and/or IgM are present in a minority of cases and usually seen in association with IgG. Immunoglobulin deposition is commonly associated with complement components C3 (Fig 3D) and C1q (Fig 3B). However, in some cases isolated C3 deposition is seen, indicating a pathogenetic role of antibody-independent complement activation.

Electron Microscopy (EM)

In addition to electron dense deposits in glomeruli (Fig. 4C), the tubulointerstitial electron dense deposits are seen in about 30-50% of kidney biopsies with lupus GN, all of which also display LM features of SLE TIN, albeit of variable severity (Schwartz et al., 1982; D'Agati, 2007). Electron dense deposits may be seen in intact tubules, damaged but non-atrophic tubules or atrophic tubules (Fig. 4A,B). These deposits involve all tubular segments including proximal convoluted tubule, distal convoluted tubule, cortical and medullary collecting ducts. The distribution of deposits is variable, ranging from few scattered deposits (Fig. 4B) to large deposits completely surrounding the tubules (Fig. 4A). The deposits are localized on both sides of basal lamina and in an intramembranous location and frequently are surrounded by layers of basal lamina. Associated findings include morphologic features of tubular epithelial cell injury such as cytoplasmic vacuolization, reduplicated and thickened tubular basal cell lamina. Focal and diffuse electron dense deposits are noticed in peritubular capillaries (Fig. 4D). These are located in

close proximity to endothelial cells, associated with reduplication of basal lamina and surrounded by newly formed basal lamina.

Immunohistochemistry

There is no role of immunohistochemistry in the diagnostic evaluation of SLE TIN. However, these studies provide insights into the pathogenesis of SLE TIN. Immunophenotypic analysis of the interstitial inflammatory cell infiltrates reveals a predominance of T lymphocytes with a lesser proportion of B lymphocytes, macrophages and natural killer cells (Boucher et al., 1986). The CD4/CD8 T cell ratio varied among studies. In a recent study, Chang et al. (2011) demonstrated that in addition to the diffuse interstitial predominant T cell infiltration, there are T and B lymphocyte aggregates containing plasmablasts, and/or germinal center-like structures containing follicular dendritic cell networks and centroblasts, in over half of renal biopsies with lupus GN with TIN. They further observed that direct immunofluorescence studies demonstrate lack of tubular basement membrane deposits in *diffuse* interstitial inflammation. However, T and B cell *aggregates* are significantly associated with tubular basement membrane immune complex deposits detected by IF.

Pathogenesis

The pathogenesis of *secondary* SLE TIN remains unknown, but probably involves both immunologic and nonimmunologic mechanism. The immunologic mechanism reflects renal injury mediated by SLE-associated, organ-specific cell- or antibody-mediated tubulointerstitial injury; whereas the nonimmunologic mechanism involves factors or pathways that are known to induce tubulointerstitial injury against the background of significant glomerular diseases of any cause. The relative contribution of these mechanisms to SLE TIN remains unknown, noting that the more specific evidence of the immunologic injury, i.e. tubular electron dense or immunoglobulin/complement deposits is noted in less than a half of renal biopsies with SLE TIN. Nevertheless, these two general mechanisms may not be mutually exclusive and perhaps share several mediators in their respective downstream pathways.

It is accepted that the glomerular immune complex deposits in lupus glomerulonephritis represent preformed circulating immune complexes composing of self antigens and their autoantibodies that get entrapped in the glomeruli (Nangaku and Couser, 2005). Alternatively, immune complex formation may occur *in situ* in the glomeruli, when a circulating antibody binds to constitutive glomerular antigens or to exogenous antigens entrapped/planted in the glomeruli. The same concepts have been implicated, with variable experimental support, in the pathogenesis of SLE TIN, and may account for the immune complex deposition in

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tubules, interstitium and peritubular capillaries in this condition.

Recent experimental evidence, however, suggests that the pathogenesis of SLE TIN may be different from that for glomerular immune complex deposition. Satoskar et al. (2011) studied the IgG subclass composition of deposits in various compartments of kidneys with lupus nephritis and noted that the IgG subclasses of deposits were different in tubular basement

membrane and vascular wall compared to glomeruli, suggesting that the mechanisms for immune complex formation in glomeruli and the tubulointerstitium are different. They hypothesized that the tubular basement membrane immune complexes may be formed *in situ* to antigens such as tubular epithelial cell DNA, histones or endogenous cellular proteins. Demonstration of B-cell clonal selection, in addition to expansion and clonal restriction in germinal center-like interstitial

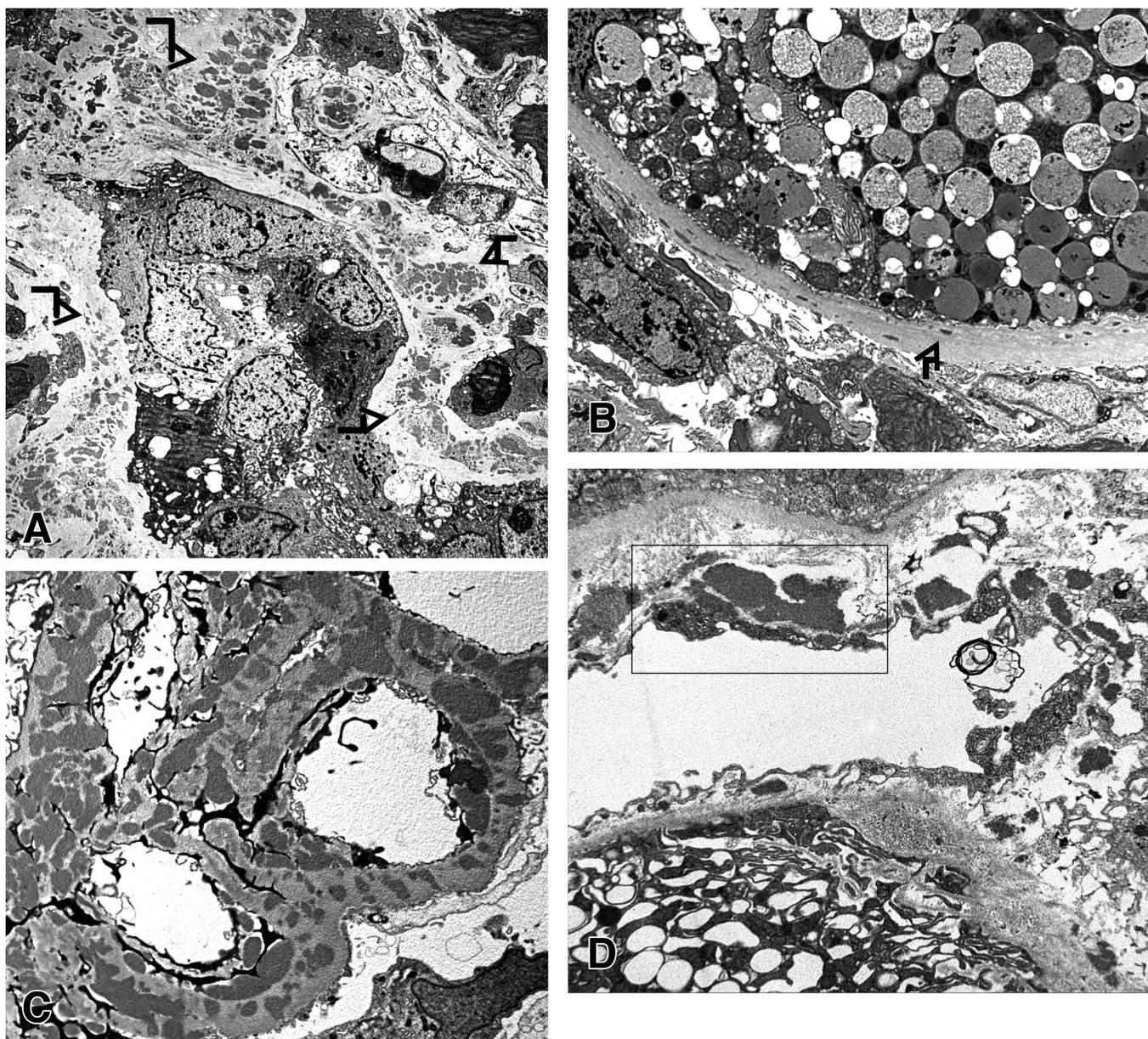


Fig. 4. Electron microscopy. **A.** Abundant electron dense deposits (arrows) along the tubular basement membranes (TBM). **B.** Scant small electron dense deposits (arrow) along the TBM. **C.** Same biopsy as in B. There are several electron dense deposits in mesangial, subepithelial, and subendothelial locations, indicating lupus Class IV and V glomerulonephritis. **D.** Electron dense deposits in a peritubular capillary (box), a rare finding. A, D, x 8,000; B, x 10,000; C, x 7,000

inflammatory cell aggregates in renal biopsies with SLE GN and TIN, indicates the presence of an in situ antigen and factors promoting the proliferation of B-cells. Lu et al. (2012) reported an overexpression of microRNAs (MiR) in lupus nephritis compared to normal controls. These MiRs were differentially expressed in various compartments of the affected kidney. MiR-638 expression was significantly higher in the

tubulointerstitium, whereas MiR 146a expression was higher in the glomeruli. Since MiRs regulate post-transcriptional modification of gene expression, a differential MiR expression suggests of diverse pathogenesis of immune complex formation in tubules and glomeruli. Furthermore, the tubulointerstitial MiR-638 expression significantly correlated with proteinuria, indicating the clinical significance of tubulointerstitial

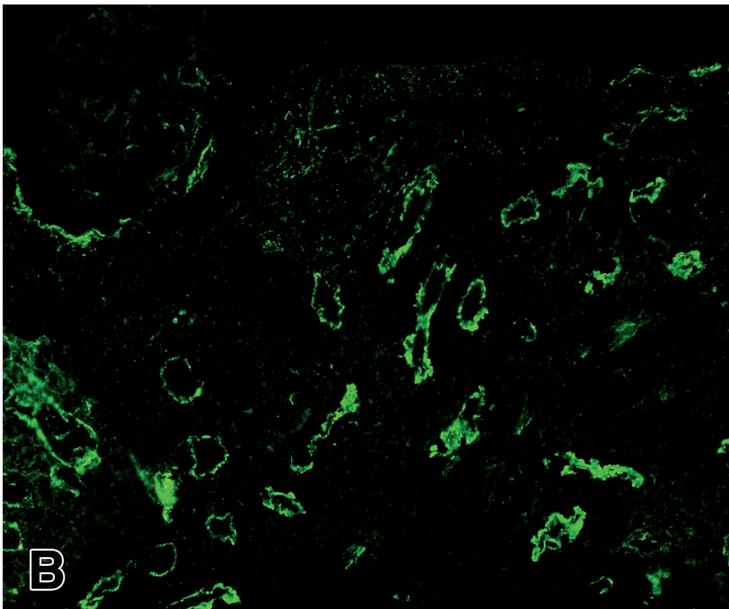
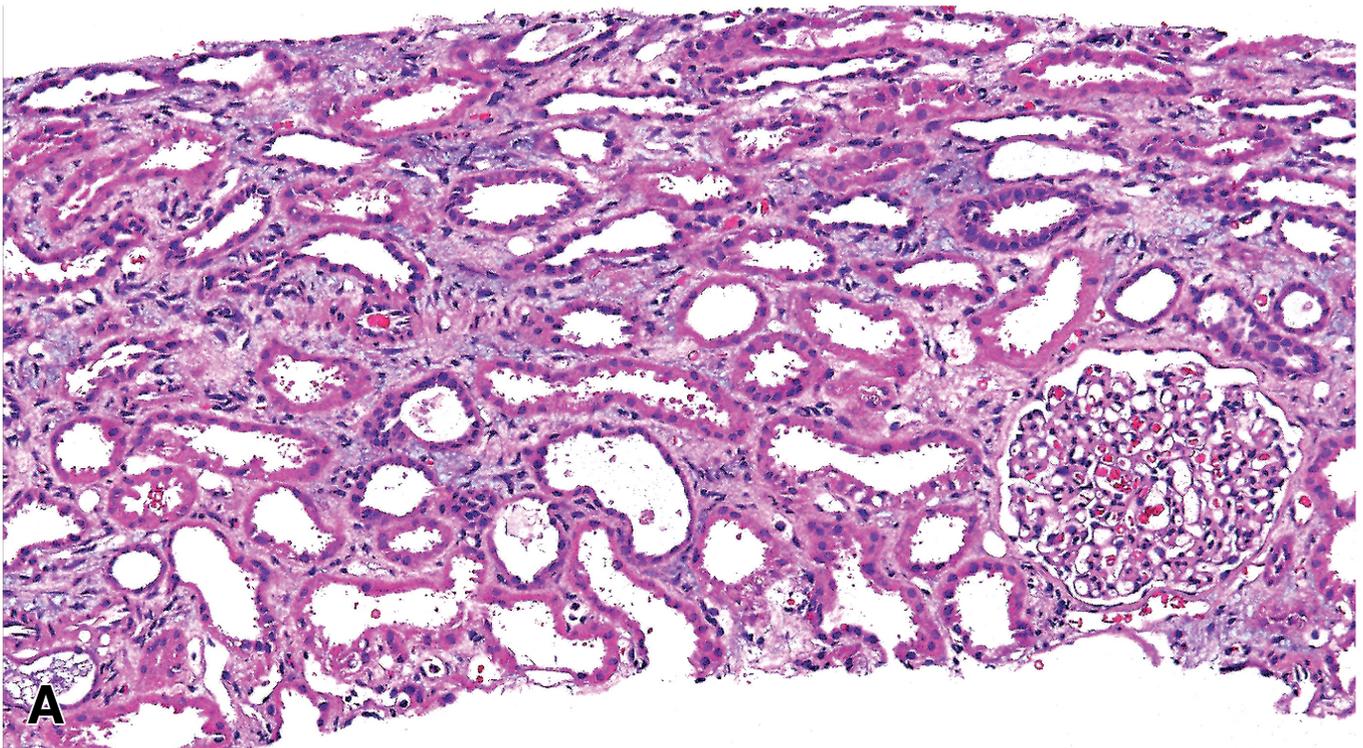


Fig. 5. Primary lupus tubulointerstitial nephritis. **A.** There are diffuse predominantly acute tubulointerstitial changes, including tubular dilatation, acute tubular cell injury, interstitial edema, early focal interstitial fibrosis, and mild interstitial mononuclear inflammatory cell infiltrates. A glomerulus, however, shows only mild focal mesangial sclerosis (H&E stain). **B.** Immunofluorescent study shows diffuse finely granular staining of the tubular basement membrane, in contrast with virtually no staining of the glomerulus (upper left). A, x 100; B, x 200

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involvement in lupus nephritis.

The tubulointerstitial lesions in lupus nephritis can develop through a nonimmunologic mechanism, including cytotoxic effect of proteinuria or an interstitial inflammatory/ischemic process induced primarily by the associated lupus GN. It is well accepted that advanced glomerular injury, regardless of type, will eventually lead to tubulointerstitial injury. The underlying mechanism is complex but involves the tubulotoxic effect of proteinuria, chronic ischemic injury, cytokine-mediated chemotaxis and cell injury. Any of these probably participate in the nonimmunologic mechanism of SLE TIN. In fact, elevation of chemokine RANTES and CCR5 (Stasikowska et al., 2007), engagement of tubular Toll-like receptor 9 (Benigni et al., 2007), or activation of transcription factor NF- κ B (Zheng et al., 2008) have all been implicated in the pathogenesis of SLE TIN.

Treatment

The optimal treatment of SLE TIN remains unknown. SLE TIN is frequently associated with lupus GN and may either affect its clinical course or carry independent prognostic implication. Yet, specific treatments aiming at this component of lupus nephritis have not been developed. Currently, it is the class of lupus GN that primarily guides the treatment, even in cases where SLE TIN is significant. In general, as per American College of Rheumatology guidelines, lupus GN Class I or Class II does not require immunosuppression for the renal manifestations. The treatment of Class III and Class IV lupus GN involves aggressive therapy with immunosuppressive agents such as corticosteroids in combination with azathioprine or cyclophosphamide. Pure class V lupus nephritis with nephrotic range proteinuria is treated with immunosuppression and Class VI lupus GN is treated with renal replacement therapy (Hahn et al., 2012). For cases presenting with renal tubular acidosis, symptomatic correction of acidemia is the mainstay of treatment, and addition of corticosteroids can help correct the acidemia (Fang and Chen, 2000).

Prognosis

Contribution of SLE TIN towards renal dysfunction in SLE patients with lupus nephritis is controversial. Since SLE TIN is often associated with significant lupus GN, the association of the tubulointerstitial injury with renal dysfunction is obscured by the presence of glomerular injury. The majority of earlier studies showed a lack of clinical or prognostic significance of tubulointerstitial disease in lupus nephritis. Schwartz et al. (1982) found a lack of association between renal function and extraglomerular immune deposits. O'Dell et al. (1985) observed that active interstitial inflammation in the renal biopsy is associated with an increased probability of doubling serum creatinine.

However, because of a high correlation of tubulointerstitial disease with diffuse proliferative lupus nephritis in their study, they concluded that tubulointerstitial disease does not add independent prognostic information and should not influence therapy. Park et al. (1986) and Jeruc et al. (2000) found no correlation between presence of tubulointerstitial immune deposits and interstitial inflammation or tubular lesions.

Recent studies, however, emphasize the prognostic significance of SLE TIN. In a series of related studies, Hill et al. (2001) found that "the tubular lesions offered the best correlation with the current serum creatinine value of any morphologic variable, as well as good correlation with outcome". Daniel et al. (2001) observed that the extent of tubular lesions is a strong predictor of renal outcome in lupus nephritis and tubular expression of cell adhesion molecules like ICAM-1 and CD40 may also serve as prognostic indicators. Howie et al. (2003) demonstrated that the extent and severity of chronic tubulointerstitial injury is a strong predictor of progression to renal failure in SLE patients. Degree and extent of tubulointerstitial lesions such as interstitial inflammatory cell infiltration, tubular atrophy, and interstitial fibrosis correlate with renal dysfunction and are independent risk factors for renal outcome (Weening et al., 2004). Most recently, Yu et al. (2010) comprehensively evaluated the clinical significance of tubulointerstitial lesions in 313 patients with lupus nephritis, and confirmed that interstitial inflammation, tubular atrophy and interstitial fibrosis are significant independent risk factors of renal outcome. Presence of higher degree of tubulointerstitial injury correlated with poor renal outcome with respect to risk of doubling of serum creatinine or end-stage renal disease.

Primary SLE TIN

The vast majority of SLE TIN is of secondary type, i.e., associated with lupus GN. However, isolated SLE TIN without glomerular changes or with minor glomerular abnormalities, e.g., Class I or Class II lupus GN, is rare but well documented. This condition is termed *primary* SLE TIN. Although only about 15 of these cases have been reported (Table 1), *primary* SLE TIN seems to have a quite homogenous and distinctive clinicopathologic features, which provides additional insights into the pathogenesis of the tubulointerstitial involvement in SLE.

Clinical Presentation

Primary SLE TIN most commonly presents as acute renal failure with or without anuria/oliguria. In one case, two episodes of acute renal failure developed four years apart, and each of them responded well to steroid therapy (Michail et al., 2003). In three cases, tubular dysfunction without proteinuria and with or without elevated serum creatinine, lead to renal biopsy (Disler et

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al., 1978; Gur et al., 1987; Ali and Al-Windawi, 2013). In two cases minimally deranged renal function against a background of active systemic lupus prompted a renal biopsy, which displayed typical features of primary SLE TIN (Makker, 1980; Omokawa et al., 2008). In most cases, there was no or minimal proteinuria, in keeping with the absence of or only minor glomerular changes (Epstein and McClusky, 1976; Cunningham et al., 1978; Tron et al., 1979; Disler et al., 1978; Makker, 1980; Gur

et al., 1987; Singh et al., 1996; Michail et al., 2003; Mori et al., 2005; Omokawa et al., 2008; Kamishima et al., 2009; Moyano et al., 2009; Ali and Al-Windawi, 2013). Nephrotic range proteinuria was, however, reported in a single case, in which there was no significant glomerular changes by LM and IF, but EM showed diffuse effacement of foot processes (Klahr and Lynch, 1980). Active urinary sediment has also been observed to be present (Epstein and McClusky, 1976; Cunningham et

Table 1. Primary lupus tubulointerstitial nephritis: clinicopathologic features.

Case	Year	First Author	Age	Sex	Clinical Presentation	Serum Creatinine (mg/dl)	Proteinuria	Tubulointerstitial Changes			Glomerular Changes	Treatment/Outcome	
								Acute	Chronic	IF			
1	1976	Epstein	52	F	AKI	6,3	2+	Yes	Yes	IgG, IgM, C3 (TBM)	EDD (TBM)	Mild mesangial cell hypercellularity	
2	1978	Disler	20	F	Hyperchloremic acidosis, RTA	Normal	<10mg/100 ml	No	Yes	C3 (TBM)	NA	Normal	Refractory to steroids
3	1978	Cunningham	30	F	AKI, oliguria	2,7	None	Yes	No	IgG, C3 (TBM, interstitium)	NA	Lupus Class II	Responded to steroids
4	1979	Tron	42	F	AKI, anuria	NA	None	Yes	No	IgG, C1q (TBM)	NA	Lupus Class II	Responded to steroids
5	1979	Tron	24	F	AKI, anuria, malignant hypertension	10,6	None	Yes	Yes	IgG, C1q, C3, IgM (TBM, vessels)	NA	Mild mesangial cell hypercellularity, mesangial C1q	Responded to dialysis and antihypertensive treatment, no steroids
6	1980	Klahr	72	M	NS, CKI	5,8	6 g/day	Yes	Yes	IgG, IgM, C3 (Interstitium)	NA	Minimal glomerular abnormalities, effacement of foot processes	Responded to steroids
7	1980	Makker	3	M	Extrarenal lupus	0,5	40 mg/day	Yes	Yes	Linear IgG, focal C1q (TBM, PTC)	No deposits	Lupus GN Class II	Refractory to steroids
8	1987	Gur	25	F	AKI, RTA	4	1.2 g/day	Yes	Yes	C3 (TBM), IgG tubular epithelial cell nuclei	No deposits	Lupus GN Class II	Responded to potassium and bicarbonate supplements for RTA. No steroids given
9	1996	Singh	59	M	AKI	5,5	0.25 g/day	Yes	Yes	IgG, IgA, IgM, C3, C1q (TBM, interstitium)	EDD (TBM, Bowman's capsule)	Normal	Responded to steroids
10	2003	Michail	30	F	AKI (2 episodes, 4 years apart)	2.1/2.2	0.48 g/day	Yes	No	IgG, C3, C1q (TBM)	NA	Mesangial hyperplasia	Responded to steroids
11	2005	Mori	64	M	AKI	2,9	0.19 g/day	Yes	Yes	IgG, C3 and C1q (TBM)	EDD (TBM)	Minimal glomerular abnormalities	Responded to steroids in each episode
12	2008	Omokawa	63	M	Extrarenal lupus	0,85	None	Yes	Yes	IgG, IgA, IgM, C1q, C3, kappa and lambda light chain (TBM, PTC, interstitium)	EDD (TBM)	Lupus GN Class II	Responded to steroids
13	2009	Kamishima	48	F	AKI	1,3	0.78 g/day	Yes	Yes	NA	NA	Normal	Responded to steroids
14	2009	Myoano	67	F	AKI	6,7	None	Yes	No	Kappa light chain (Tubulointerstitium)	NA	Normal	NA
15	2013	Ali	38	M	AKI, RTA	1,3	1 g/day	Yes	No	IgG, IgA, C3, C1q (TBM, PTC)	NA	Normal	Responded to steroids

AKI, Acute kidney injury; CKI, Chronic kidney injury; EDD, Electron dense deposits; EM, Electron microscopy; GN, Glomerulonephritis; IF, Immunofluorescence; NA, Not available; NS, Nephrotic syndrome; PTC, Peritubular capillaries; RTA, Renal tubular acidosis; TBM, Tubular basement membrane

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al., 1978; Klahr and Lynch, 1980; Gur et al., 1987; Singh et al., 1996; Michail et al., 2003; Ali and Al-Windawi, 2013; Kamishima et al., 2009). All patients had active SLE at time of renal biopsy diagnosis.

Morphologic Findings

Light microscopy

The changes involve predominantly the tubules and interstitium and may be acute and/or chronic. Compared to secondary SLE TIN, these changes displayed the same morphologic spectrum; however, the acute changes are virtually constant and often are the exclusive or predominant component (Fig 5A). The glomeruli, in contrast to the cases of secondary SLE TIN, are either unremarkable (at least 7 cases) or displayed only mild mesangial changes including mesangial hypercellularity and immune deposits consistent with lupus GN Class II (Table 1).

The acute tubular injury includes tubular epithelial cell necrosis, desquamation of tubular epithelial cells, tubulitis (intraepithelial lymphocytic infiltration) and lysis of tubular basement membrane along with presence of luminal granular casts. Chronic tubular injury includes tubular atrophy and luminal hyaline casts. The acute interstitial injury includes interstitial lymphoplasmacytic infiltration, interstitial edema and peritubular capillaritis. Mixed inflammation with significant neutrophil infiltration has been reported in one case (Singh et al., 1996). Lymphoid follicles have also been observed (Omokawa et al., 2008). The interstitial inflammation is often diffuse, rather than patchy (Tron et al., 1979; Singh et al., 1996; Michail et al., 2003; Omokawa et al., 2008; Kamishima et al., 2009). The chronic interstitial injury includes interstitial fibrosis and loss of peritubular capillaries.

Although acute tubulointerstitial changes have been noted in each case, these changes were exclusively present in at least five cases (Cunningham et al., 1978; Tron et al., 1979; Michail et al., 2003; Moyano et al., 2009; Ali and Al-Windawi, 2013;). In addition the remaining cases showed concomitant chronic tubulointerstitial changes.

Immunofluorescence

IF study reported in 14 cases, showed tubulointerstitial deposits of immunoglobulins and/or complement in each case. Glomerular deposits were not seen or limited to the mesangium (Fig 5B). Almost all cases displayed a granular pattern, but a linear pattern, which has not been described in secondary SLE TIN, was reported in one biopsy from a 3-year-old boy (Makker, 1980). The deposits were often limited to the tubular basement membrane (Epstein and McClusky, 1976; Cunningham et al., 1978; Tron et al., 1979; Disler et al., 1978; Klahr and Lynch, 1980; Makker, 1980; Gur et al., 1987; Singh et al., 1996; Michail et al., 2003; Mori

et al., 2005; Omokawa et al., 2008; Moyano et al., 2009; Ali and Al-Windawi, 2013), with concomitant interstitial deposits seen in at least 4 cases (Cunningham et al., 1978; Omokawa et al., 2008; Singh et al., 1996; Moyano et al., 2009). Isolated interstitial deposits were seen ((Makker, 1980; Omokawa et al., 2008; Ali and Al-Windawi, 2013), and deposits in the wall of small vessels (Tron et al., 1979) were also reported.

The deposits were composed of immunoglobulins and complement components in 11 cases. Isolated C3 was reported in two cases (Disler et al., 1978; Gur et al., 1987), and isolated kappa light chain in one case (Moyano et al., 2009), but other typical features of primary SLE TIN were noted in each of these three cases. Among the immunoglobulins, IgG was constantly observed to be present (Fig. 4b) (Epstein and McClusky, 1976; Cunningham et al., 1978; Tron et al., 1979; Klahr and Lynch, 1980; Singh et al., 1996; Makker, 1980; Michail et al., 2003; Mori et al., 2005; Omokawa et al., 2008) with concomitant IgM (Epstein and McClusky, 1976; Tron et al., 1979; Singh et al., 1996; Michail et al., 2003; Omokawa et al., 2008) and IgA (Singh et al., 1996; Omokawa et al., 2008; Ali and Al-Windawi, 2013) in few cases. Among the complement components, C3 is most frequent (Epstein and McClusky, 1976; Cunningham et al., 1978; Tron et al., 1979; Disler et al., 1978; Klahr and Lynch, 1980; Makker, 1980; Gur et al., 1987; Michail et al., 2003; Mori et al., 2005; Omokawa et al., 2008; Ali and Al-Windawi, 2013), followed by C1q (Tron et al., 1979; Makker, 1980; Singh et al., 1996; Michail et al., 2003; Mori et al., 2005; Omokawa et al., 2008; Ali and Al-Windawi, 2013). In fact, C1q was the only observed complement component in one case (Tron et al., 1979). C4 was surprisingly not reported in any case.

Electron microscopy

EM study was reported in six cases. Electron dense deposits were noted in four of them and they were present along tubular basement membrane (Epstein and McClusky, 1976; Singh et al., 1996; Mori et al., 2005; Omokawa et al., 2008). Deposits were not seen in two cases in which IF study showed *linear* IgG or only C3 along the tubular basement membrane. Electron dense deposits were not observed in the interstitium, blood vessels, or peritubular capillaries in any of the cases.

Pathogenesis

Primary SLE TIN is most probably immune complex mediated, since immunoglobulin and complement deposits along tubular basement membrane was noted in each of the reported cases. This pathogenetic pathway is further supported by the presence of active SLE with several autoantibodies in all cases. Pathogenetic enigma remains however. The nature of the responsible antigens is not known. These could be native but nonrenal or exogenous antigen trapped in the

tubular basement membrane (Singh et al., 1996; Michail et al., 2003). Alternatively, these could be native tubular basement membrane antibodies, since, at least in one case, there were linear immune deposits along the tubular basement membrane concomitant with circulating anti-tubular basement membrane antibodies.

A rare case hints at additional pathogenetic route. Cell-mediated immunity perhaps also plays a role, at least a permissive one. Omokawa et al (2008) found that the interstitial inflammatory infiltrates were composed predominantly of CD8-positive cytotoxic T cells, suggesting a role of cell-mediated immunity. In addition, they also observed B-cell rich lymphoid follicles in the interstitium and a predominance of IgG4-positive plasma cells along with minor IgG1- and IgG3-positive plasma cells, in the peritubular interstitium and along the tubular basement membrane, suggesting an association with IgG4- related TIN. Regardless of the nature of the pathogenic antigens and their immune responses, how these responses are limited almost entirely to the tubulointerstitial compartment remains unanswered.

Treatment and prognosis

Steroids appear to be the mainstay treatment for primary SLE TIN, with no case requiring aggressive cytotoxic treatment. Response to moderate/high-dose steroids was observed in 9/13 cases with reported clinical follow-up. In one of them this response was maintained during two distinct disease episodes four years apart. The prognosis of primary SLE TIN therefore appears to be excellent (Cunningham et al., 1978; Tron et al., 1979; Klahr and Lynch, 1980; Makker, 1980; Singh et al., 1996; Michail et al., 2003; Mori et al., 2005; Omokawa et al., 2008; Kamishima et al., 2009; Ali and Al-Windawi, 2013). Two cases were steroid-refractory (Disler et al., 1978; Makker, 1980). One of them presented with renal tubular acidosis and focal C3 deposits along tubular basement membrane (Disler et al., 1978). In the other case of a 3-year-old child with extra-renal lupus and mild proteinuria, with diffuse *linear* IgG and focal C1q along tubular basement membrane, the extra-renal lupus responded to steroid, however the renal function and urinalysis remained unchanged over a period of 2 years (Makker, 1980). Steroid was not used in two cases, both of which features acute renal failure and one also with renal tubular acidosis. However, clinical response was achieved with dialysis and antihypertensive treatment in one (Tron et al., 1979), and with treatment for renal tubular acidosis (potassium and bicarbonate) in the other (Gur et al., 1987).

Conclusion

Tubulointerstitial injury is increasingly recognized in the spectrum of lupus nephritis. Secondary SLE TIN is quite frequent, clinically protean, and now of unequivocal therapeutic and prognostic impact. Primary SLE TIN is rare but displays a distinctive

clinicopathologic profile including a favorable prognosis. In spite of these profound clinical implications, the current review underlies a limited knowledge on the pathobiology of SLE TIN. Further study and understanding in this area would undoubtedly enhance the management of lupus nephritis, which currently focuses only on the glomerular involvement.

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