Rare transformation in repeat renal biopsies suggests a different pathogenesis of segmental and global lesions in proliferative lupus nephritis

Vladimir Tesar

Correspondence and offprint requests to: Vladimir Tesar; E-mail: vladimir.tesar@vfn.cz

Heterogeneous histological findings in the renal biopsies of patients with systemic lupus erythematosus were distinguished early into different types of lupus nephritis with different outcomes. The effort to unify the terminology resulted in six classes of the World Health Organization (WHO) classification published in 1982 [1]. Having apart biopsies with normal histology (Class I) and advanced sclerotic lesions (Class VI), it became apparent that there are two main types of lupus nephritis: membranous (Class V) and proliferative (Classes III and IV), although there were also patients with a combination of both membranous and proliferative lesions. Membranous lupus nephritis was shown early to have better outcome than proliferative lupus nephritis, but the relation between focal (Class III) and diffuse (Class IV) lesions remained uncertain.

Segmental lesions typical for Class III lupus nephritis resemble the lesions present in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and are very different from global lesions typical for Class IV which, on the other hand, may resemble the immune complex-mediated lesions present, e.g. in idiopathic membranoproliferative glomerulonephritis. According to the new International Society of Nephrology/Renal Pathology Society (ISN/RPS) histological classification [1] segmental lesions may be present both in Class III (focal lupus nephritis) if affecting <50% of glomeruli and in a special subclass of Class IV (diffuse lupus nephritis) called IV-S if affecting >50% of glomeruli. The ISN/RPS Class IV category thus mixes together segmental (diffuse lupus nephritis) called IV-S if affecting >50% of glomeruli and in a special subclass of Class IV (diffuse lupus nephritis) called IV-G if affecting >50% of glomeruli [2].

Although some authors argued that focal segmental lesions may evolve into diffuse global lesions and both of them may regress (after treatment) into mesangial (Class II) lupus nephritis, other authors referred that there are significant differences between WHO Classes III and IV (and ISN/RPS Class IV-S and IV-G) lupus nephritis both concerning the histological characteristics, clinical presentation and outcome, and that the pathogenesis of segmental and global proliferative lesions may be different [3].

In this issue of NDT Pagni et al. evaluated 142 patients with lupus nephritis and repeat biopsies. Although their original main aim was to look at the role of repeat renal biopsies in routine clinical practice, their paper also adds an important contribution to our understanding of the putatively different pathogenesis of different histological classes of (proliferative) lupus nephritis. Patients with IV-G class of lupus nephritis had, at presentation compared with segmental forms of lupus nephritis (Classes III and IV-S), higher proteinuria, serum creatinine and blood pressure and more mesangial proliferation, wire loops and tuft necrosis in the biopsy. The disease was more severe in both first and repeat biopsy in Class IV-G compared with Class III and IV-S patients and repeat renal biopsy predicted better trend of serum creatinine and proteinuria than the first biopsy. Most importantly, although the transitions between different histological classes were quite frequent (40.8%), the transition between segmental (III/IV-S) and mesangial (II/IV-G) forms was extremely rare, strongly suggesting that really both forms may have not only different clinical and histological features, but also different pathogenesis.

Important differences in the histology between IV-G and IV-S patients were repeatedly (and relatively consistently) described. Patients with IV-S class had, compared with IV-G class, e.g. fewer glomeruli with wire loops [3, 4] and hyalin thrombi [3], more frequent fibrinoid necrosis [4–7], lower endocapillary proliferation [6], significant trend to the higher proportion of crescents [4], less frequent infiltration of glomeruli with monocyte/macrophages, lower interstitial inflammation [6] and less IgG (or even complete absence of IgG) on immunofluorescence [3].

Histologic differences may be translated into some differences in the clinical presentation. Class IV-G lupus nephritis was shown to present, compared with Class IV-S, with higher serum creatinine, worse proteinuria [4–6] and higher diastolic blood pressure [4, 7] and also lower C3 [5, 6] and lower proportion of patients with the positivity of anticoagulopin antibodies [6]. Patients with Class III were also shown to have a lower prevalence of the positivity of anti-C1q compared with Class IV patients [8] and patients with segmental lesions (Classes III and IV-S) have the lowest levels of complement factor H in SLE and lupus nephritis patients [9].
There is much more controversy concerning the impact of segmental versus global lesions on the outcome of the patients. Although some studies suggest that patients with a high proportion of segmental lesions (WHO Class III with the involvement of >50% of glomeruli [10]) and especially the patients with more densely distributed segmental lesions [11] may have poorer response to treatment and outcome compared with WHO Class IV patients [10], or more specifically patients with diffuse global lesions [11] and another study demonstrated, on the opposite, worse 10-year renal outcome of IV-G compared with IV-S patients [12], most other studies [4, 5] as confirmed by the recent meta-analysis [13] did not find any difference in the outcome between patients with IV-S and IV-G classes of LN.

Many studies mostly using older WHO classification reported very frequent transformation between different classes of lupus nephritis [14–17] ranging from 26 to 75% of repeat renal biopsies [16, 18]. Early studies reported frequent transformations between WHO Classes III and IV [16, 19], which were at that time believed to be a part of the same continuum of proliferative changes. On the other hand, in another study in patients rebiopsied to discern the cause of increasing proteinuria [17], none out of 20 patients with Class IV switched to Class III and none of 8 patients with Class III switched to Class IV.

Newer study using the ISN/RPS classification [20] reported also class switch during the flare of the diseases in as many as 49% of instances, the most frequent being the switch from non-proliferative (Class V) to proliferative lesions as confirmed in other studies [9]. Switch between Classes III and IV was, however, not so uncommon, 5 patients out of 28 patients with Class IV switched to Class III and 5 out of 6 patients originally with Class III switched to Class IV, the absence of clear distinction between IV-S and IV-G classes prevents direct comparison with the commented paper by Pagni et al.

Type of transformation clearly depends on the indication of the repeat biopsy; more active lesions were found in biopsies performed in patients with renal flare compared with protocol biopsies (or postmortem examination [21]) where usually milder forms of lupus nephritis (Class II or V) prevailed [14, 15, 22]. Active proliferative lesions (both IV-S and IV-G) have a higher rate of transformation to inactive Class II lesions compared with active/chronic lesions [7]. There is usually an increase in the chronicity index in the studies where rebiopsy was performed during the flare of the disease [18]. Progression of the disease in the renal biopsy cannot be reliably predicted based on the clinical and laboratory and baseline histological parameters [9, 18].

Pagni et al. suggest that pauci-immune lesions present in IV-S patients resemble the lesions present in systemic vasculitis, although ANCA positivity even in patients with Class IV-S lupus nephritis is infrequent [3]. In some patients ANCA-associated necrotizing and crescentic glomerulonephritis (mostly with p-ANCA and anti-MPO positivity) may occur superimposed on lupus nephritis [23]. Crescentic lupus nephritis (>50% of glomeruli affected by crescents) was diagnosed in 21% of patients with Class IV-G lupus nephritis [24]. Patients with crescentic lupus nephritis had higher frequency of ANCA and significantly poorer 4-year outcome compared with other IV-G patients. Although the pathogenesis of segmental and global proliferative changes, as corroborated by the paper by Pagni, may really be different we are, unfortunately, still far from its full understanding.

Another important point also discussed in the paper of Pagni et al. is the clinical utility of repeat renal biopsies.

First of all, repeat renal biopsies were repeatedly shown (in a similar way as in the paper of Pagni et al.) to have some prognostic value [13, 18, 22, 25, 26], although the data are rather controversial. Repeat renal biopsy at 6 months had a good predictive power possibly as a measure of a good response to the therapy [22] and not responding patients were clearly at risk of progression probably due to persistent inflammatory reaction despite treatment. Two studies looked at the prognostic value of repeat biopsy during a flare and both showed a prognostic value of high chronicity index [25, 26] in terms of doubling serum creatinine [26]. Persistence of IV-G lesions on protocol repeat biopsy, half a year after the initiation of the treatment was associated with higher blood pressure, higher proteinuria, deteriorating renal function and lower serum C3 levels [15]. Moreover, persistence of IV-G lesions on repeat biopsy had much worse outcome than patients with persistent IV-S lesions [22]. In a randomized controlled trial (see below) information derived from protocol repeat biopsies after 2 years had, however, in multivariate analysis no added predictive value [18] compared with serum creatinine.

In many studies repeat renal biopsy were also used to demonstrate the efficacy of treatment. The chronicity index increased in patients with high-dose prednisone only and remained unchanged in patients on the combination of steroids and cytotoxic drugs [6]. Recently, protocol renal biopsies at 2 years did not demonstrate any difference between patients with proliferative lupus nephritis treated after cyclophosphamide induction with either mycophenolate mofetil or azathioprine as a maintenance treatment [27]. Most patients improved and had ISN/RPS Classes I/II/V at follow-up and less patients stayed at Class IV. Activity index decreased and chronicity index slightly, but significantly, increased with no difference between both limbs.

Protocol renal biopsy at 2 years demonstrated similar decrease of the activity index in patients treated with either cyclophosphamide or azathioprine as induction treatment of proliferative lupus nephritis, but there was a significantly greater increase of the chronicity index in patients treated with azathioprine [18]. Interestingly, although there was, in the azathioprine limb compared with the cyclophosphamide limb, a higher relapse rate and early tendency to the higher percentage of doubling of serum creatinine [17] it was not translated into any significant difference in the sustained doubling of serum creatinine, end-stage renal disease and mortality after a long median follow-up of 9.6 years [3]. Persistence of proliferative lupus nephritis in the protocol repeat biopsy after 2 years of the treatment was associated with higher serum creatinine and greater proteinuria [18], but in the multivariate analysis only serum creatinine at enrolment and after 2 years was the predictor of outcome, none of the histopathological variables (either at entry or at 2 years) significantly added to the prediction of outcome.

Many authors have recommended repeat biopsies to guide the treatment of lupus nephritis [4, 13, 26, 28]. It is generally agreed that it is difficult to reliably assess the activity (and putative transformation) of lupus nephritis based on the currently available clinical and laboratory markers [29, 30] and
renal biopsy should thus help with therapeutic decision especially in patients during the flare of the disease.

In most papers, including the paper by Pagni, rebiopsy was performed in the case of suspected relapse of the disease and the physicians would supposedly modify (augmented) the treatment of their patients even without having the information on the histological activity of the disease. The real contribution of repeat biopsy when performed during the flare of the disease to the clinical decision-making may thus not be so high as suggested by some of these authors. As the transformation from non-proliferative to proliferative lupus nephritis is frequent, most authors recommend to consider rebiopsy during a flare or with increasing proteinuria and serum creatinine specifically in patients with non-proliferative (Class V) lupus nephritis [10]. In patients with proliferative lesions on a primary, biopsy transformation is improbable and repeat biopsy may only help to distinguish between active and chronic lesions.

It has been well documented that the response of active proliferative lupus nephritis to any kind of currently available treatment is very slow and that the mean time to remission is ∼10 months [31]. Long persistence of the insufficiently suppressed inflammatory changes in glomeruli may apparently contribute to the higher risk of the future progression to the end-stage renal disease, which still occurs in 15–20% of patients with proliferative lupus nephritis [32]. Using repeat renal biopsy we could be able to identify these poorly responding patients and either prolong the induction (initial) treatment or switch to cyclophosphamide or vice versa as recommended in the recently published EULAR/ERA-EDTA guidelines on treatment of lupus nephritis [9].

Information from protocol repeat renal biopsies performed in all patients with proliferative lupus nephritis before the switch from the induction (initial) treatment to the maintenance one would thus be apparently very valuable. As we have, however, no good evidence how to proceed in the case of both insufficiently tamed (or even progressive) and in very well-responding lupus nephritis with only minimal residual activity, these protocol biopsies should be considered only as a part of well-defined randomized controlled trials or at least well-defined observational studies.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Pagni et al. The value of repeat biopsy in the management of lupus nephritis: an international multicentre study in a large cohort of patients. *Nephrol Dial Transplant* 2013; 28: 3014–3023.)

REFERENCES

Bone disease is frequently observed in chronic kidney disease (CKD) and increases a patient’s risk for fracture, cardiovascular (CV) calcification and mortality. The Kidney Disease Improving Global Outcomes foundation defined a new syndrome incorporating the bone, mineral and CV disorders, such as chronic kidney disease–mineral and bone disorders (CKD–MBDs) [1]. The relationship between the bone turnover and CV disease is well documented in patients with CKD [2], as is the relationship between low bone density and aortic calcification in patients without CKD [3]. The quest for a modifiable reliable biomarker of CV and bone disease in CKD–MBD remains the nephrologist’s Holy Grail. In recent years, numerous bone proteins have been associated with the outcome in patients with CKD, such as osteoprotegerin (OPG) [4], fibroblast growth factor (FGF)-23 [5], bone-specific alkaline phosphatase (bsALP) [6] and, more recently, sclerostin.

Sclerostin is a glycoprotein (22 kDa) product of the SOST gene in osteocytes, which inhibits osteoblast and bone formation. The canonical Wingless-type mouse mammary tumour virus integration site (Wnt) pathway has a bone anabolic and mineral and bone disorders (CKD–MBD) 


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Sclerostin in CKD-MBD: one more paradoxical bone protein?

Guillaume Jean*
and Charles Chazot

Correspondence and offprint requests to: Guillaume Jean;
E-mail: guillaume-jean-crat@wanadoo.fr

Department of Dialysis, NEPHROCARE Tassin-Charcot, Sainte Foy-Les-Lyon, France

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Bone disease is frequently observed in chronic kidney disease (CKD) and increases a patient’s risk for fracture, cardiovascular (CV) calcification and mortality. The Kidney Disease Improving Global Outcomes foundation defined a new syndrome incorporating the bone, mineral and CV disorders, such as chronic kidney disease–mineral and bone disorders (CKD–MBDs) [1]. The relationship between the bone turnover and CV disease is well documented in patients with CKD [2], as is the relationship between low bone density and aortic calcification in patients without CKD [3]. The quest for a modifiable