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Editorial Comments

No lupus nephritis in the absence of antiC1q autoantibodies?

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One of the characteristics of systemic lupus erythematosus (SLE) is the large inter- and intra-individual variability of the clinical course. Lupus nephritis is no exception. Some patients with kidney involvement may show rapid progression to renal failure, while others may enter complete and stable remission after adequate therapy. More difficult to manage are the large number of patients who have similar clinical and histological patterns at presentation, but alternate periods of clinical quiescence with renal relapses of different severity. It is still uncertain which, if any, immunologic parameters may help to diagnose a renal flare. The increase in anti double-stranded DNA (dsDNA) titre or hypocomplementaemia related to classical pathway activation provides no indication as to whether a relapse includes the kidney. Here we review the evidence, which has accumulated over the last few years and appears to indicate that antiC1q autoantibodies (antiC1q Ab) may help in distinguishing a renal from a non-renal relapse under certain circumstances.

Classical pathway of complement activation

C1q, the first component of the classical pathway of complement activation, contains six distinct globular heads and a unique collagen-like region. Several functions have been assigned to C1q. They include principally the initial step of complement activation by the binding of the globular heads of the C1q molecule to the Fc portions of immune complexes and the participation in the clearance of self antigens generated during programmed cell death [1,2]. Autoantibodies to C1q were first identified in the serum of patients with SLE, as 'C1q precipitins' [3]. A more detailed analysis followed over the years, and it is now well established that antiC1q Ab are mostly of the IgG isotype and the epitopes recognized are on the collagen-like region (CLR) of C1q [4]. IgG antibodies to CLR/C1q were quantitated in serum by ELISA, using purified human CLR or whole C1q as antigen and they provide almost identical results [5,6]. Studies of the prevalence of IgG antibodies to CLR/C1q have reported low frequencies in normal healthy donors (3–5%); however, there is an increase with age [7]. Several reports have indicated that 30–50% of sera from patients with SLE contain antibodies of the IgG isotype reactive with human C1q [4,8–10]. Interestingly, antiC1q Ab have also been found in a small group of patients presenting a disease profile close to SLE, but having as the main clinical sign urticaria [hypocomplementaemic urticaria vasculitis syndrome (HUVS)] [11,12]. The prevalence of antiC1q Ab is increased in some other autoimmune diseases, so that they are unlikely to be of help in the diagnosis of SLE, except perhaps when they suggest under the appropriate circumstances HUVS.

SLE and antiC1q antibodies

In SLE, antiC1q Ab have been found to be associated with low complement and lupus nephritis, but not with a general score of disease activity [4,13]. Although there is no evidence that antiC1q Ab can directly activate complement in a normal serum, these Ab are somehow linked to complement activation *in vivo* since they best correlate with a low C1q [14]. The second association is more directly of clinical interest: almost all patients reported to have a severe lupus nephritis (WHO III/IV) or a relapse of nephritis had antiC1q Ab at the time of the renal involvement [10,15–17]. This finding does not stem from one report only, but appears to be a general finding in many studies that have addressed this point. In addition, clinical signs of renal involvement were found to be associated with significantly increased serum titres of anti C1q Ab in

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the 6 months preceding the renal relapse [18]. Interestingly, when compared with antiC1q Ab, an increase in the anti dsDNA level was associated with all forms of relapses in SLE patients but did not single out the renal relapses [19]. Recently, Trendelenburg *et al*. [20] presented direct evidence for a lack of occurrence of severe lupus nephritis among antiC1q antibody negative patients. None of the patients who were negative for antiC1q antibodies had or developed active nephritis. These data should however be put into perspective. Gunnarsson *et al*. [21] have recently reported that only 11 out of 18 patients with biopsy-proven lupus nephritis had antiC1q Ab. However, they reported simultaneously that C1q was low in most of these patients and correlated inversely with antiC1q Ab ($P < 0.0009$), suggesting the presence of antiC1q below the detection limit. In fact the same group had reported that in all of six patients with proliferative lupus nephritis they could find peripheral B-cell producing specific antiC1q Ab, but did not find such Ab in the serum of all six patients [22]. This illustrates that standardization of the antiC1q Ab assay is required. For instance, in another report, a result for antiC1q Ab was reported as positive only when it exceeded the normal range +5 standard deviations (SD) as compared with the usual 2 SD [23]. This emphasizes an important aspect, which is that from a clinical point of view only the absence of antiC1q Ab may have an impact for the management of the patients. Since recurrence of lupus nephritis is highly unlikely in the absence of these antibodies, aggressive treatment can be tailored accordingly. Thus, a regular follow-up of antiC1q Ab could be proposed. A word of caution comes from isolated reports of no antiC1q Ab in patients with pure membranous glomerulonephritis (WHO V) or with an anticardiolipin syndrome associated with major renal damage. Thus, the presence of antiC1q might be a component of lupus nephritis excluding membranous nephritis (WHO V) and other renal lesions, which might occur during the progression of the disease. On a pathophysiological basis we may speculate that antiC1q Ab are necessary, but not sufficient, for producing the immune damage in the glomeruli since many individuals with SLE or HUVS have high titres but no renal involvement on a clinical basis. Interestingly, lupus nephritis is characterized by the deposition of C1q along glomerular and tubular basement membranes [24] and Mannik and Wener [25] showed that antiC1q are to be found in the same deposits. Figure 1 shows the characteristic C1q distribution in a renal biopsy studied by direct immunofluorescence in a patient with class V (WHO classification) glomerulonephritis, which is identical to IgG deposition. The sum of these observations would suggest that C1q and the antiC1q autoAb are one of the central elements in severe lupus nephritis.

Ideally, the diagnosis of renal flares should be based on kidney biopsy, but because of its potential complications, this invasive procedure cannot be repeated too frequently. Thus the monitoring of antiC1q Ab after the diagnosis of SLE might be helpful and represents a non-invasive biological marker in the follow-up of SLE patients. When the measurement shows no such Ab, the likelihood of severe lupus nephritis (stage III/IV) is low. However, only time and practice will tell whether these initial observations based on clinical studies are directly of help to the clinician.

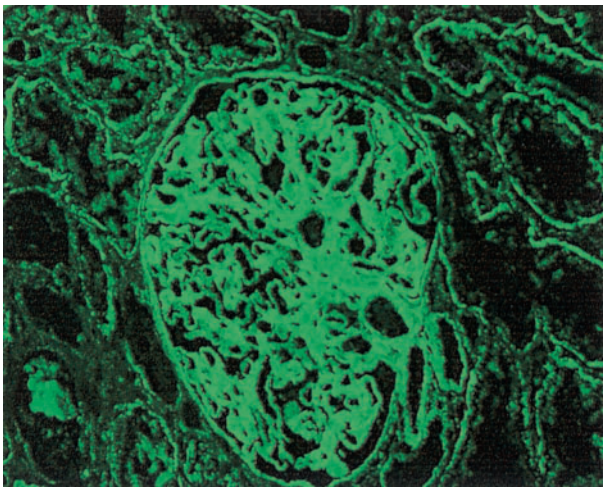

Fig. 1. Direct immunofluorescence of C1q deposition along glomerular and tubular basement membrane in a patient with lupus glomerulonephritis (class V). Magnification: ×400.

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