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Review Article

Lupus Podocytopathy, Literature Review

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Abstract

Lupus podocytopathy is a recently described phenomenon characterized by diffuse foot process effacement without peripheral capillary wall immune deposits and glomerular proliferation. It has been described in systemic lupus erythematosus patients with nephrotic syndrome in case reports and a few series. The term of lupus podocytopathy denotes that it as lupus nephritis-related phenomenon, however, the theory of coexisting minimal change disease is also a possibility. Each theory has its own supporting clinical and pathological facts. This literature review is made for a comprehensive analysis of the available clinical circumstances and histological data of the reported cases. Also, it elaborates on the pathological background for both diseases process. The aim of this review is to reach an optimum categorization of this phenomenon.

Keywords: Lupus podocytopathy, Nephrotic syndrome, Lupus nephritis, Minimal change disease, Electron microscopy, Systemic lupus erythematosus.

INTRODUCTION

Since the introduction of the first attempts of Lupus nephritis (LN) classification, namely the WHO classification, the nephrotic syndrome was a clinical manifestation of WHO Class IV and/or V, [1]. Even with the release of the International Society of Nephrology (ISN) Classification of LN by 2004, the nephrotic syndrome was under the umbrella ISN Class IV and/or V [2]. These two classes in both classification systems require immune complex deposition along the peripheral capillary wall as an essential diagnostic pathological finding. However, numerous cases of systemic lupus erythematosus (SLE) with nephrotic syndrome in the absence of peripheral immune deposition and with evident diffuse podocytes foot process effacement are being reported. These cases are not addressed in either of the classification systems. The repeated encounters of this phenomenon by many authors merit further analysis and investigation. This phenomenon may represent a coexisting two disease processes namely Minimal change disease (MCD) and LN. Also, there is a possibility that the podocyte injury is part of lupus nephritis which leads to the development of the terminology; Lupus podocytopathy.

REVIEW

In 1990, Trachman H reported a case of an 18 - year old female with mesangial LN, who developed nephrotic range proteinuria with spontaneous remission after six weeks and negative history of non-steroidal anti-inflammatory drug (NSAID) exposure [3]. Also, in 1997, DR. James P Lash described two patients with SLE, presented with nephrotic syndrome. Both showed mesangial proliferation, immune complex deposition on direct immunofluorescence (DIF) and electron microscopy (EM) in addition to more than 50% of the podocytes showed foot process effacement. However, NSAID usage was reported in both cases [4]. These few reported cases raise the question about the offending pathological factor behind the development of nephrotic syndrome in those patients. Could this be explained merely by LN, or there should be another coincidental pathology, namely MCD.

To answer this question, the clinical circumstances and the pathological findings of such cases need to be elaborated. For example, the possibility of coincidental MCD needs to be considered in the presence of a positive history of NSAID exposure which has a well-described association with MCD [5].

This is furtherly supported by a case described by Y-T Wang *et al*., which was about a 14- year old girl who had SLE for eleven months and developed nephrotic syndrome preceded by NSAID exposure which had been prescribed for joint pain. Her renal biopsy showed MCD with no immune complex deposition except for trace mesangial IgM, which is not an unusual finding in MCD. Furthermore, remission was achieved with steroid followed by one episode of a relapse upon steroid tapering managed successfully by a full dose of steroid combined with Cyclophosphamide [6].

More papers addressed a similar picture with a larger number of cases. In 2002, a small series eighteen patients with SLE, full-blown nephrotic syndrome and pathological findings of MCD or Focal segmental glomerulosclerosis (FSGS) were described by Dube *et al.*, and Heritage *et al.*, All the patients with MCD experienced rapid remission with steroid while those with FSGS showed variable response to steroid, [7, 8]. By 2005, Kraft *et al*., described a subset of SLE patients who developed nephrotic-range proteinuria without evidence of either glomerular peripheral capillary immune complex deposits or endocapillary proliferation, and had complete or near complete podocyte foot process effacement on EM [8].

In term of the temporal relationship between the onset of SLE and NS, it was observed that the patients presented with the nephrotic syndrome early in the disease course, soon after the onset of symptoms and the diagnosis of SLE in the majority of cases in both Kraft *et al*., and Hertig *et al.*, [8, 9]. This close temporal relationship seems to call for the interpretation that the podocyte injury is a result of active LN more likely than the coexistence of two separate but concurrent diseases; SLE and MCD.

However, a long-term interval between the SLE diagnosis and the onset of NS has been also reported. The case reported by T. Sugimoto *et al*., showed a 25- year gap between the diagnosis of SLE and the onset of NS [10]. Also, eleven months interval was noticed in the case reported by Y-T Wang et al and more than 10 years elapsed for the NS to develop in one of the two cases of SLE patients reported by Dr. Tim J. Vyse [6, 11]. This long- term interval contradicts well with the findings of close temporal relationship between the onset of SLE and development of NS mentioned previously, which may argue against the idea of lupus podocytopathy and favor the coexistence of two disease process.

Hu *et al.*, is the largest cohort study addressed this phenomenon, it described 50 patients with the assumed diagnosis of lupus podocytopathy. It illustrated representative data on clinical presentations, treatment responses, and relapse rates in patients with this entity. All of the studied patients had fully- developed nephrotic syndrome with ≥50% (and in most patients, >70%) foot process effacement. In addition to that, thirteen patients had normal light microscopy findings, twenty-eight demonstrated mesangial proliferation and nine had FSGS lesion. Mesangial immune deposits confirmed by DIF and EM were found in 47 of the 50 patients. Regarding the treatment response, the remission rate with immunosuppressant was 94% among all the groups, however, the median time to remission was similar in the MCD group and mesangial proliferative groups; four weeks, in comparison to eight weeks in the FSGS group. As with podocytopathies not associated with SLE, relapse rates were high (56%) and did not differ by histologic pattern. The striking similarity in clinical presentation, remission rates, rapidity of remission, and relapse rates in the MCD and mesangial proliferative subgroups raise the question of whether it is appropriate to use the same umbrella term of lupus podocytopathy for these two patterns of glomerular injury [12]. The criteria for the diagnosis of lupus podocytopathy proposed in this study are shown in Table-1.

Table-1: Clinical and Morphological Criteria for Lupus Podocytopathy

1. Clinical: the diagnosis of SLE; nephrotic range proteinuria, often accompanied by AKI, and no history of nephrotoxic medications (e.g., NSAIDs) prior to the onset of renal disease. 2. Light microscopy: glomerular minimal change, mesangial proliferation, or focal segmental glomerulosclerosis patterns without subepithelial or subendothelial deposits. Excluding glomerular scar of proliferative lupus nephritis in the FSGS pattern. 3. Immunofluorescence: the absence of capillary immune deposition with or without Ig and complement deposition in mesangial areas. 4. Electronic microscopy: FPE.50%, typically FPE.70% with mesangial dense deposits and in the absence of subepithelial or subendothelial dense deposits.[a] To diagnose lupus podocytopathy, all four criteria should be met.[b]
NSAID, nonsteroidal anti-inflammatory drugs; FPE, foot process effacement. [a] Occasional isolated subepithelial or subendothelial dense deposits may be visible. [b] Few cases may present with preclinical SLE at the onset of the disease and should be carefully followed up.

It is difficult to delineate the pathogenesis of lupus podocytopathy since the pathological mechanism of MCD is not well- understood. However, most of the authors concurred about the rule of the circulating cytokine; IL-13, this factor has been suggested based on its experimental overexpression in rats which caused diffuse effacement of foot process on ultrastructural examination [13-17]. Also, this factor has been implicated in Hodgkin's lymphoma which has a well-describe clinical association with MCD [16]. The IL-13 is abnormally released by the aberrant T helper cells and the cross-reaction between the T helper cells and the renal dendritic cells may result in direct damage to the podocytes in MCD [13, 14]. Animal studies revealed that IL-13 alters the podocytes and causes MCD by downregulation of podocin, nephrin and dystroglycan and upregulation of B7-1 in the glomeruli [15]. Aberrant activation of T helper cells and uncontrolled release of numerous cytokines including IL-13 has been implicated also in the pathogenesis of SLE [9]. Abnormal T- cell activation is the common pathological ground for the development of SLE and MCD.

CONCLUSION

From all of the aforementioned reports and the cohort study, we can find that based on the common pathological background for both disease conditions, the frequently reported close temporal relationship and the preexisting mesangial immune complexes (which defines LN ISN Class I and /or II), one may argue that this podocyte injury is basically an SLE- related process and further modification to the current ISN classification of LN is required to include this entity. On the other hand, the long- term interval between the onset of the two disease conditions, positive history of previous exposure to NSAID products as well as the successful remission with steroid therapy alone and frequent relapse reported by the majority of cases may favor the theory of a coincidental MCD. Therefore, each case with this phenomenon needs to be evaluated thoroughly with more attention directed toward the medication history, exclusion of associated hematolymphoid disorders and renal biopsy to reach an optimum categorization of the disease process and subsequently an optimum management.

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