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Mini Review

Extracapillary glomerulonephritis: Is there any relationship with diabetes? A literature review

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Abstract

Glomerular crescents may be observed in conditions other than typically rapidly progressive glomerulonephritis such as antiglomerular basement membrane disease, pauci-immune glomerulonephritis and lupus nephritis. Data on extracapillary glomerulonephritis (ECGN) in diabetic patients are limited. In this study, we have discussed whether ECGN in diabetic patients is an independent or anatomo-clinically associated with diabetes.The presence of glomerular crescents in a diabetic patient can sometimes be clearly attributed to an independent classic cause. Diabetic Nephropathy seems to be a possible cause. The pathogenesis of crescent formation in diabetic nephropathy is unknown. In most cases, the renal prognosis is pejorative despite aggressive immunosuppressive therapy. The presence of crescent in a diabetic patient without any clear cause may represent a variant phenotype of diabetic nephropathy which leads to rapid decline in Glomerular Filtration Rate and ultimately to End-Stage Renal Disease. There are still several limitations to the current studies, such as the small sample sizes, which tend to give inadequate representation; making them more hypothesis-generating than confirmatory. Large clinical and immunopathological studies with a broad spectrum of disease severity will be required to ascertain whether such presentations represent a distinct pathogenic phenotype of DN. Exploring the relationship between crescent formation and diabetic glomerulosclerosis is needed to completely uncover the mechanism of the non-inflammatory crescent formation.

Keywords: Diabetes, Extracapillary, Crescent, Glomerulonephritis, Kidneys

Introduction

Cellular crescents are typically associated with various forms of rapidly progressive glomerulonephritis such as antiglomerular-basement membrane disease (GBM), pauci-immune glomerulonephritis, and lupus nephritis.[1,2] Crescents, however, may also be observed in other conditions. They have been documented in a wide variety of glomerular diseases including IgA nephropathy and Alport syndrome.[1,3] The presence of such a lesion may lead to rapid decline in Glomerular Filtration Rate and ultimately to End Stage Renal Disease (ESRD).[4]

Although crescent formation in diabetes is rare, their presence raises the suspicion for a coexisting disease such as pauci-immune glomerulonephritis.[5] Therefore, some reports indicate that crescents, as a pathological component of rapidly progressive glomerulonephritis, may appear in the glomeruli of diabetic patients with or without diabetic glomerulopathy.[6] There have been occasional case reports of "crescents" in Diabetic Nephropathy (DN).[7-9] There are few case series of crescentic GN due to diabetes.[1,10] The Renal Pathology Society classifies diabetic nephropathy according to the type of glomerular lesion. However, there is no reference to glomerular crescent formation in diabetic nephropathy.[11] As of now, published literature has paid little attention to extracapillary glomerulonephritis in diabetic patients. Understanding this particular presentation could improve the management and the prognosis of diabetic patients with such pathological findings. Here, we make a review of the literature on the topic; whether ECGN in diabetic patients is an independent or diabetes associated anatomoclinical presentation.

Renal Biopsy in Diabetic Patients

In diabetic patients with overt proteinuria, a diagnosis of diabetic kidney disease can be made in the appropriate clinical setting without pathological confirmation in cases with diabetic retinopathy, long

standing diabetes, and hypertension.[12] On the other hand, performing a renal biopsy on diabetic patients has usually been considered when the presence of renal disease other than diabetic kidney disease is suggested by clinical signs, such as the rapid deterioration of renal function, the detection of microscopic or macroscopic hematuria, or the presence of proteinuria in newly diagnosed diabetics without any retinopathy or neuropathy.[6,12] When performed, renal pathology can show glomerular crescents.

Presumably Diabetes-Unrelated Crescent GN

The presence of crescents in renal biopsy specimens of diabetic patients may have served to stimulate a search for causes other than diabetes.[10] In some cases, the presence of an extracapillary glomerulonephritis in the renal biopsy of a diabetic patient can be clearly attributed to an independent cause instead of diabetes. Such cases have been described previously as shown in Table 1.

Diabetes Presumed to be the Cause of Crescent GN

Glomerular crescents have rarely been reported in patients with diabetic glomerulopathy.[7-9] It is not known why glomerular crescents in diabetic nephropathy have only been rarely observed. One possible explanation is that kidney biopsies in diabetes are reserved for patients with atypical presentations and other primary glomerular diseases.[4] Previously, in case report studies, some authors have reported possible association of crescentic lesions with diabetic nephropathy.

Table 1. Summary of Previous Studies on Crescent GN Presumed Not Related to Diabetes

Author	Study design (number of cases)	Year	Pathology	Laboratory findings	Presumed cause
Syed R et al.[13]	Case report (*n* =1) with Review article	2015	-Diffuse crescentic glomerulonephritis -Pauci-immune type	-ANA, hepatitis and HIV serologies, ASLO andanti-GBM: negatives -Complement levels: normal -PR3 ANCA: positive	ANCA vasculitis
Nasr SH et al.[6]	Case series (*n* =23)	2008	-ANCA-associated Pauci-immune Necrotizing and Crescentic GN -and Diabetic GS	-ANCA positive: (18/23) pANCA (16), cANCA(2) -ANCA: negative (4/23), -Unknown (1)	-Drug -ANCA vasculitis
Nishijima R et al.[14]	Case report (*n* =1)	2005	-Spike of GBM -Crescentic GN -nodular glomerular lesions +arteriolar hyalinization -Diffuse Granular IgG, C3 deposition on capillary loops and mesangium	-pANCA: positive -Anti-GBM: negative -Others relevant immunological tests: not available	Not available (but not associated to diabetes)
Takeshita Y et al.[15]	Case report (*n* =1)	2000	-Crescentic GN -No deposit on IF	-Serum IgG, IgM, IgA, C3, C4, and C1q were all normal. -pANCA: positive	Microscopic Polyangiitis
Kawamoto S [16]	Case report (*n* =1)	2011	- Crescentic GN - Pauci-immune on IF	-pANCA: positive - Other immunological tests : negative	ANCA vasculitis
Ahuja TS et al.[17]	Case report (*n* =1)	1998	-Diffuse and nodular glomerular sclerosis -Sharp linear deposits of IgG	-ANA, rapid plasma reagin, ANCA, hepatitis B and C screening: negative. -Serum complement levels : normal	anti-GBM nephritis
Ninomiya T et al.[18]	Case report (*n* =1)	2002	-Nodular diabetic glomerulosclerosis -Fibrous and fibrocellular crescents no sign of vasculitis -No deposit	-ANA, hepatitis B and C screening : negative -Serum C3 and C4 levels : normal -pANCA: positive	ANCA glomerulo-nephritis

ANCA: Anti-neutrophil cytoplasmic antibodies, pANCA : Perinuclear ANCA (MPO), cANCA (PR3): Cytoplasmic ANCA, GN: Glomerulonephritis, GS: Glomerulosclerosis, GBM: Glomerular basement membrane, C3: Complement component 3, IF: Immunofluorescence, ANA: Antinuclear antibodies, HIV: Human immunodeficiency virus, ASLO: Antistreptolysin O antibodies, PR3: Proteinase 3, Ig: Immunoglobulin, C1q: Complement component 1q, C4 : Complement component 4.

Elfenbein and Reyes [10] reported a correlation between the frequency of crescents and severity of diabetic renal disease. The percentage of crescents also correlated with increased blood urea nitrogen and serum creatinine. Nevertheless, their study has several limitations; of course, whether some of these patients represented cases of diabetes with superimposed crescentic glomerulonephritis secondary to ANCA, anti-GBM disease, or other causes is unknown since the study was completed in 1975 when ANCA anti-GBM testing were unavailable. Later, some studies suggested the probable association between diabetes with or without diabetic glomerulosclerosis and crescent GN, diabetes being the presumed cause as shown in Table 2.

Table 2. Summary of Previous Studies on Crescent GN Presumed Related to Diabetes

Author	Study design (number of cases)	Year	Diagnosis	Laboratory findings	Presumed cause
Toth [8]	Case report (*n* =1)	1987	-Crescent GN -No fibrin no GBM breaks	-AntiGBM: negative -C3 and C4: normal	Diabetes
Otani et al.[7]	Case report (*n* =1)	2012	-diabetic nodular glomerulosclerosis with crescent -no evidence of vasculitis, fibrinoid necrosis, or GBM breaks	-ANCA, ANA antiGBM: all negative -viral serologies: negative	Diabetes
Gaut et al.[5]	Case report (*n* =2)	2014	diabetic nodular glomerulosclerosis with crescents	-Normal C3, C4 -ANCA and anti-GBM antibodies were negative -HIV, hepatitis C, and hepatitis B negative	Diabetes
Ko YS et al.[19]	Case report (*n* =1)	2016	Advanced diabetic glomerulosclerosis with crescents	-Negative Cryoglobulinemia -Negative ANCA and anti-GBM antibodies were negative -HIV, hepatitis C, and hepatitis B negative	Diabetes

ANCA: anti-neutrophil cytoplasmic antibodies, GN: glomerulonephritis, GBM: glomerular basement membrane, C3: complement component 3, ANA: Antinuclear antibodies, HIV: Human immunodeficiency virus, C4: complement component 4.

Crescent in Diabetic Nephropathy: What Could be the Explanation?

The pathogenesis of crescent formation in diabetic nephropathy is unknown. According to Elfenbein and Reyes (1975), the rare occurrence of crescent formation in diabetes could be related to "exudative lesions," or "fibrin caps" (hyaline caps). This could be attributed to the fact that they are more highly correlated with the severity of diabetic vascular disease than the degree of mesangial expansion.[10]

Theoretically, the eventual rupture of the glomerular basement membrane stems from the sheer stress placed on the capillary wall of a hyaline cap rather than from inflammatory damage, such is the case for immune-mediated glomerulonephritides. Hyaline caps occur at sites of mesangiolysis and capillary aneurysm formation. Therefore, Mottl et al. could not establish the link between mesangiolysis or hyalinosis and extracapillary hypercellularity.[4]

In 2012, Otani et al.[7] reported a case of a 53-year-old male who had suffered from type 2 diabetes for 11 years presented with generalized oedema with decreased renal function and massive proteinuria. In a biopsy, nine of 17 glomeruli contained crescents on the ground of diabetic glomerulosclerosis. No clinical clues suggested any alternative cause of the crescents.

Gaut et al.[5] catalogued the cellular composition of glomerular crescents in diabetic nodular glomerulosclerosis and compared the expression of nephrin and claudin1 with that in inflammatory-crescents-containing glomeruli, crescent-free diabetic glomeruli, and normal-appearing glomeruli. Crescentic cells in diabetes manifested claudin 1 or nephrin. Nephrin-positive cells in diabetic crescents significantly increased as compared to inflammatory crescents, whereas there was a decrease in the glomerular tuft in diabetes, with or without crescents.

Due to the limited number of participants in the

conducted researches, the suggestion of claudin 1 and nephrin staining as differentiation markers singling out inflammatory crescents from pseudo-crescents must be interpreted with caution. Further investigations using greater numbers of cases is needed to determine the clinical utility of this observation.[20]

What are the Clinical Implications?

According to previous reports, diabetic patients with glomerular crescents can manifest severe kidney failure, hematuria and proteinuria. Elfenbein and Reyes (1975) observed that the presence of crescents in diabetic glomerulosclerosis was correlated with the level of creatinine and the extent of proteinuria. Mottl et al. reported that the presence of crescent in Diabetic Kidney Disease is predictive of time to ESRD.[4]

The presence of crescent in a diabetic patient without any clear causemay represent a variant phenotype of diabetic nephropathy that leads to rapid decline in GFR and ultimately to ESRD. Available studies have several limitations, including the small sample sizes studies provided by single institutions. Thus, the collected data turn out to be more hypothesis-generating than confirmatory and will, thereby, require re-examination using larger datasets and immunopathological tools in order to elucidate the exact relation between diabetes and crescent formation in the absence of a clear classic cause.

Conclusion

The presence of glomerular crescents in a diabetic patient can sometimes be clearly attributed to an independent classic cause. DN seems to be a possible independent cause. Large clinical and immunopathological studies with a broad spectrum of disease severity, will be required to ascertain whether such presentations represent a distinct pathogenic phenotype of DN. To completely uncover the mechanism of the non-inflammatory crescent formation, one is expected to explore the relationship between crescent formation and diabetic glomerulosclerosis.

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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