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Original contribution

Vascular mesangial channels in human nodular diabetic glomerulopathy☆,☆☆

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Summary The presence of vascular mesangial channels has been reported in idiopathic nodular glomerulosclerosis and diabetic glomerulopathy. However, only limited information on the morphology and immunohistochemical phenotype of these channels is available. This study aims to describe the light and electron microscopic features of these channels and delineate their immunohistochemical phenotype. Thirty-eight cases of human nodular diabetic glomerulopathy with mesangial channels identified by light microscopy were prospectively selected (2010-2012). The cases were stained with CD31/periodic acid–Schiff combined stain. Selected cases were immunostained for CD34, podoplanin, ERG, and Ki-67. Frequent, small and peripheral vascular mesangial channels were seen in all cases, whereas larger and more centrally located vascular channels were also observed. Communication between peripheral capillary loops and peripheral vascular mesangial channels was seen as was communication between peripheral and central vascular mesangial channels. The vascular mesangial channel lining cells showed a typical endothelial phenotype with strong expression of CD31, CD34, and ERG by immunohistochemistry. The lymphatic channel marker podoplanin was negative in all channels, and the proliferation marker Ki-67 showed no evidence of increased proliferation. By electron microscopy, mesangial channels show angulated, irregular borders with lining cells compatible with endothelium and surrounded by mesangial matrix. No basement membranes were identified surrounding the mesangial channels. These findings support the existence of vascular mesangial channels in nodular diabetic glomerulopathy and suggest neovascularization and altered blood flow within these glomeruli.
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1. Introduction

The normal glomerular tuft is a compact capillary plexus supplied by a single afferent arteriole, which branches to form the glomerular tuft upon entry into Bowman capsule. From there, several lobules form, composed of a profusion of focally anastomosing capillaries that invest an arborizing supportive mesangial stalk. This complex of capillaries eventually converges to form a single efferent arteriole that exits Bowman capsule between the primary branches of the afferent arteriole.

Diabetes mellitus is known to produce neomicrovascular proliferations. Arteriolar neovascularity has been noted at the vascular pole in nodular diabetic glomerulopathy where

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clusters of small efferent arterioles can often be observed and are believed to connect to the glomerular tuft [1]. In addition, within the mesangial nodules of diabetic glomerulopathy and in idiopathic nodular glomerulosclerosis, channels have been described that appear to connect with the capillary lumina. Markowitz et al [2] have shown that CD34-positive immunostaining cells line these channels. In this report, we expand upon previous observations by using an expanded profile of immunohistochemical stains, supplemented by ultrastructural observations, to further elucidate the origin and nature of the lining cells, their connections within the glomerular tuft, and possible relationship with hilar neoarteriolar formation.

2. Materials and methods

A total of 38 renal biopsies were prospectively selected (F. G. S.) from routine renal biopsy service over a 2.5-year period (2011-2013) and represented 22% (38 of 172 biopsies) of all diagnosed diabetic nephropathy. Inclusion criteria required the presence of (1) diabetes mellitus, (2) diabetic glomerulopathy stage III or higher, and (3) vascular mesangial channel (VMC) formation visible by light microscopy [3]. VMCs were defined by the presence of luminal structures of varying caliber embedded within mesangial matrix/mesangial nodule and often lined by endothelial-appearing cells (Fig. 1A). This study was performed in accordance with our institutional review board's policies and procedures for renal biopsy and nephrectomy specimens.

All biopsies underwent standard renal biopsy processing to include light and immunofluorescence [4,5]. Paraffin sections cut at 3 μm were stained with hematoxylin and eosin (H&E), Jones methenamine silver, Masson trichrome, and periodic acid–Schiff (PAS) reagent. Direct immunofluorescence was performed using 5-μm-thick frozen sections incubated for 1 hour with fluorescein-tagged polyclonal rabbit anti-human antibodies to IgG, IgA, IgM, C3, C1q, albumin, fibrinogen, and κ and λ light chains (Dako, Carpinteria, CA). Thirty-five biopsies had adequate tissue for electron microscopy. Formalin-fixed tissue was rinsed and postosmicated (2% aqueous OsO_4) with microwave assist for 10 minutes then processed routinely for embedment in Epon 812. Unstained thin sections were analyzed using a JEOL JEM-1011 electron microscope (Jeol, Tokyo, Japan).

Paraffin sections from all biopsies were immunostained with antibodies against platelet endothelial cell adhesion molecule CD31 (clone 1A10; Dako) at a dilution of 1:200 and counterstained with a conventional PAS reagent to enhance detection of VMCs. Additional immunohistochemical staining was performed on 10 select cases for early hematopoietic cell and vascular-associated marker CD34 (clone QBEnd/10; Vector Laboratories, Burlingame, CA) at a dilution of 1:500, erythroblast transformation specific–related gene ERG (clone EPR3864(2); Abcam, Cambridge, UK), lymphatic endothelial cell marker podoplanin (clone D2-40; Covance, Princeton, NJ), and cellular proliferation marker Ki-67 (clone MIB-1; Dako). Heat-induced epitope retrieval was performed using Tris/EDTA for CD31, CD34, and ERG and sodium citrate for podoplanin and Ki-67. After rinsing, sections were loaded onto an Autostainer Plus (Dako) and incubated with the primary antibodies for 30 minutes. Binding of CD31, CD34, podoplanin, and Ki-67 was detected with EnVision mouse and localized with DAB Plus (Dako) according to the manufacturer's protocol. Binding of ERG was detected with Ultravision Quanto Detection System HRP DAB (Thermo Fisher Scientific, Waltham, MA). Positive controls were performed on all immunostains with CD31 using normal renal parenchyma and requiring visualization of endothelial, cytoplasmic staining within the vasculature. For CD34, D2-40, and Ki-67, human tonsil was used as a control. For CD34 and D2-40, the presence of characteristic cytoplasmic vascular or lymphatic endothelial signal was seen, whereas characteristic high positive rate within germinal centers for Ki-67 was visualized. For ERG, endothelial nuclear signal was identified within myometrial tissue. Negative controls were performed for all immunostains as well, with no significant false-positive staining identified.

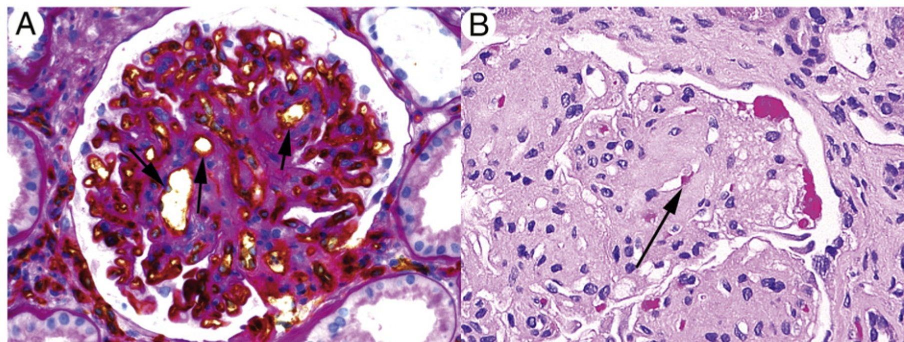

Fig. 1 A, PAS/CD31 combined stain showing staining of peripheral capillary loops and vascular mesangial channels (arrows) (original magnification, ×200). B, Peripheral vascular mesangial channel showing an intraluminal red blood cell (arrow) (H&E stain, ×600).

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