The role of renal vascular endothelial-mesenchymal transition in systemic lupus erythematosus associated thrombotic microangiopathy

Weixin Hu, Ying Zhou, Yinghua Chen, Mingchao Zhang, Shaoshan Liang, Fan Yang , Yiyao Tu, Hao Bao, Zhihong Liu

National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of medicine, Nanjing, China

Objectives:

- To investigate the phenotypic changes of renal vascular endothelial cells and its relationship with the vascular injury and renal interstitial fibrosis in patients with systemic lupus erythematosus associated thrombotic microangiopathy (SLE-TMA).

Methods:

- Biopsies from 30 SLE patients which showed lupus nephritis and renal vascular TMA were included in this study.
- Renal vascular TMA lesions were divided into acute and chronic TMA according to histology by light microscopy, normal renal tissue from nephrectomized kidney of renal cancer was used as normal control.
- The expression of renal vascular endothelial CD31,VE-cadherin,α-SMA and TGF-β were stained with immunofluorescence and immunohistochemical assays, and computer-assisted image analysis Image-Pro-Plus 6.0 and ImageScope (Aperio) were used to quantitatively analyze the intensity of endothelial marker expression recorded as the mean density (MD, integral optical density/ area of vascular endothelial layer) and the extent of renal interstitial fibrosis respectively.

Results:

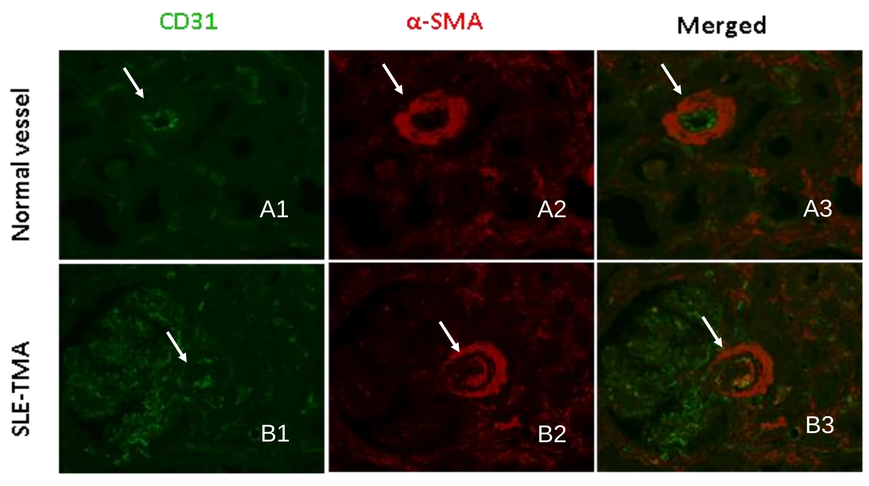

Fig1. Double immunofluorescence staining of endothelial CD31 and α-SMA

Normal renal arteriole showing continuous linear expression of endothelial CD31(green A1,3) without α-SMA expression(A2). Renal arteriole with TMA showing decreased and discontinuous endothelial CD31 expression(B1) and increased α-SMA expression(B2); A large number of cells are co-expressed with CD31 and α-SMA in the endothelial layer and in the sub-endothelial area (B3, yellow). A few cells in the glomerulus and peritubular capillaries are also co-expressed with CD31 and α-SMA. (×400)

Table 1. The association between the expression of renal vascular endothelial markers and vascular lesions

Markers	Normal vessel (n=20)	Acute TMA (n=20)	Chronic TMA (n=20)
CD31	0.45±0.06**#	0.38±0.09*	0.32±0.10
VE-cadherin	0.36±0.03**#	0.30±0.08	0.26±0.06
a-SMA	0**##	0.28±0.05	0.32±0.04

The data in the table are mean density(MD) of renal vascular endothelial markers TMA.

Chronic TMA vs normal vessel, acute TMA, *：p<0.05，：P<0.01**

Acute TMA vs normal vessel, chronic TMA, #：p<0.05，##：P<0.01

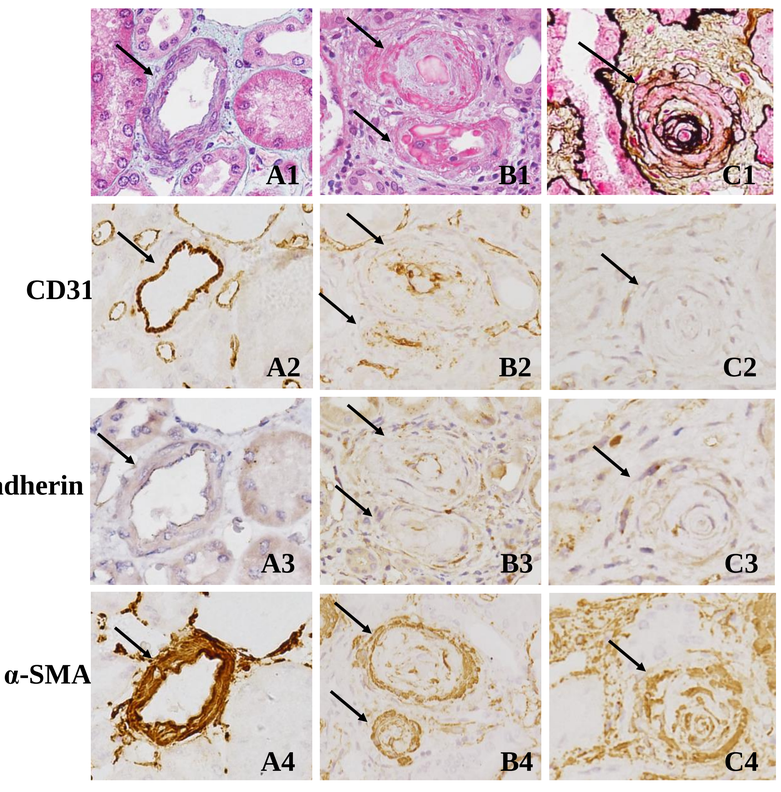

Fig2. Immunohistochemical staining of endothelial markers(×400)

Normal renal arteriole showing continuous expression of endothelial CD31(A2) and VE-cadherin(A3) and negative endothelial α-SMA(A4). Acute TMA showing decreased and discontinuous endothelial expression of CD31(B2) and VE-cadherin(B3) and increased expression of α-SMA(B4). Chronic TMA showing lower expression of CD31(C2) and VE-cadherin(C3) and higher expression of α-SMA(C4) than acute TMA. Endothelial markers in vessels with TMA are expressed both in the endothelial layer and in the sub-endothelial area. (×400)

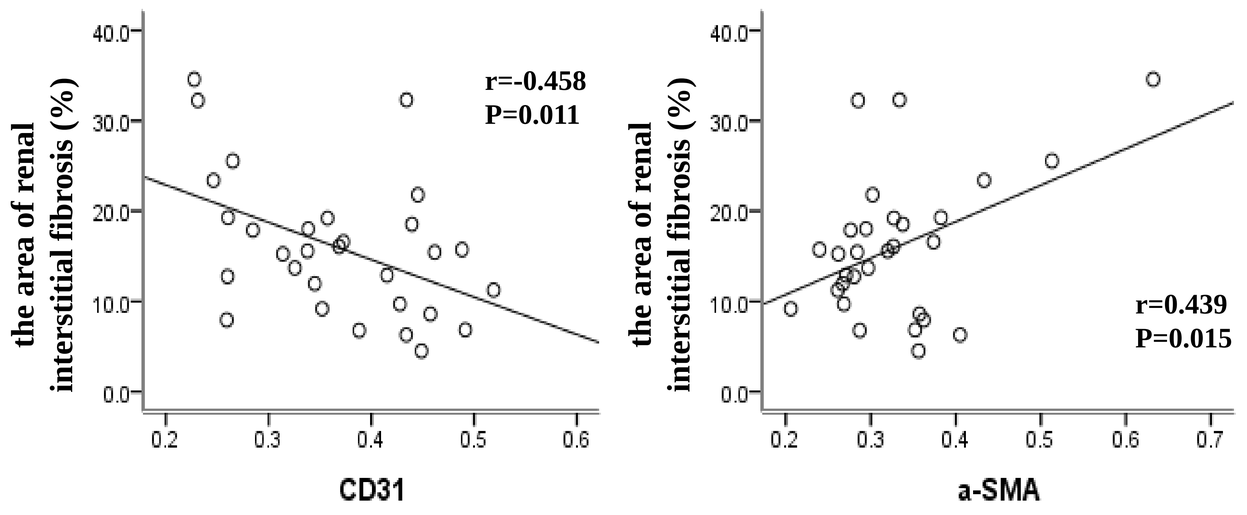

Figure 3. The association between the expression of renal arteriolar endothelial markers and the area of renal interstitial fibrosis

- **The impact of renal arteriolar endothelial α-SMA expression on the treatment response:** **After 3 months treatment, 22 of 30 lupus nephritis patients with TMA responded to the treatment and 8 patients had no response to the treatment. Then we measured the MD of CD31, VE-cadherin and α-SMA in endothelial cells of TMA vessels. Logistic regression analysis revealed α-SMA was the risk factor of the non-response of the recent treatment (P=0.023). With each 0.01 rise of the expression in a-SMA, the risk of non-response improved 1.21. Likewise, with each 0.1 rise, the risk of non-response improved 6.59. After the correction of the baseline level of SCr, α-SMA was still the risk of the non-response of the recent treatment.**

Conclusions:

Renal arteriolar endothelial to mesenchymal transition was demonstrated in SLE patients with TMA, which was associated with the endothelial and interstitial fibrosis.

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