Decreased vascular endothelial growth factor expression in focal segmental glomerulosclerosis lesions of patients under sirolimus

Helena Viana, Fernanda Carvalho, José Reinaldo Pinto, Maria João Galvão, Ana Santos, Fernando Niolasco, João Ribeiro Santos
Serviço de nefrologia, Hospital de Curro Cabral, Lisboa, Portugal.

A: Vascular endothelial growth factor (VEGF) is essential in the glomerular filtration barrier

- The vascular endothelial growth factor (VEGF) is essential in the vascular permeability, angiogenesis and cellular survival in different tissues.
- In glomeruli (GL), the podocyte (PD) synthesizes VEGF and endothelial cell-expressed VEGF.
- The VEGF acts on endothelial cells and mediates functions such as vascular permeability and endothelial cell division. In addition to its permissive role in endothelial cells, VEGF has an autocrine function that is required for podocyte survival and differentiation.
- Several studies documented that minimal alterations in glomerular (GL) VEGF expression play a pathogenic role in initiating GL disease. It is clear that interaction between podocytes and endothelial cells is critical in the filtering CKD.
- In-vivo data also show that the reduction of VEGF is associated with proteinuria (PT).
- Recent reports indicate that women with preglomerulonephritis present elevated soluble VEGF receptor 1, an inhibitor of VEGF. In a significant percentage of nephrology’s patients the anti-VEGF antibody therapy leads to proteinuria.

B: Sirolimus can cause proteinuria and FSGS lesions by a reduction of VEGF expression in the glomerulus.

- Corticosteroid inhibitor (CSI) therapy has been identified as an important non-immunological cause of Chronic Allograft Nephropathy (CAN), the most prevalent cause of late kidney transplant failure.
- Switching from CSI to sirolimus (SRL), when CAN is engrafted, has become a frequent practice but is complicated by proteinuria (PT) in a significant percentage of cases.
- The pathological mechanisms behind the proteinuria is still unclear.
- The PT withdrawal led to an increase of PT and an increased intra-glomerular pressure, which supports the hypothesis that hemodynamic changes play a significant role.
- FSGS has been related frequently as the GL lesion in these patients with CAN. FSGS has also been related to real transplant patients who were treated in vivo with SRL, without any medical history of FSGS in their native kidneys.
- A recent study reports a severe increase of PT after conversion from cyclosporine to SRL after kidney transplantation.
- These cases suggest a direct effect of SRL as a cause of proteinuria.

Objectives

According with the described in A+B+C:

- Sirolimus can cause proteinuria and FSGS lesions by a reduction of VEGF expression in the glomerulus.
- To determine if glomerular lesions and proteinuria in SRL patients could be related to altered VEGF expression.

Material and Methods

We employed indirect immunohistochemistry in paraffin-embedded sections using a mouse monoclonal antibody against VEGF-A, an inhibitor of VEGF.

Group A: Normal VEGF expression in GL Group C: Proteinuria lesions in native kidney

Group B: Proteinuric lesions in allograft kidney under SRL

Group D: Reduced VEGF expression in hypertrophied PD

Group E: Normal VEGF expression in hypertrophied PD

Results

We found that the controls (A) and B showed normal VEGF expression, with strong podocyte staining. The VEGF expression in the group C was similar to the control groups, although no FSGS lesions were observed in the studied glomeruli.

Group D showed normal VEGF expression in the apparently normal glomeruli, hypertrophied podocytes with decreased expression and detachment of podocytes.

Group E showed a normal expression of VEGF in the apparently normal glomeruli, and no staining in different lesions.

We observed a gradual reduction of VEGF expressions with progressive detachment of podocytes.

In the group E the VEGF was globally reduced, with some hypertrophied podocytes expressing decreased VEGF.

Conclusions

We confirmed the diminished VEGF expression in injured podocytes of sirolimus patients.

This decreased expression may result from a direct effect of sirolimus and provoke the appearance of FSGS lesions and proteinuria.

Further studies are needed with greater number of cases and controls, including early biopsies of patients under sirolimus.

References:

Indication

- This decrease in VEGF expression may result from a direct effect of sirolimus and provoke the appearance of FSGS lesions and proteinuria.

- Further studies are needed with greater number of cases and controls, including early biopsies of patients under sirolimus.