22-082

CIRCULATING ENDOTHELIAL CELLS AND VASCULITIS

Woywodt A, Streiber F, de Groot K, Haller H, Haubitz M. Hannover, Germany.

Objective: To demonstrate the presence of circulating endothelial cells in ANCA-associated small-vessel vasculitis, characterize their phenotype and relate the number of circulating endothelial cells to disease activity measured with the Birmingham Vasculitis Activity Score (BVAS).

Methods: 18 patients with active ANCA-associated vasculitis, 20 patients in remission, 20 healthy controls and 12 patients with non-ANCA glomerular disease were studied. Endothelial cells were isolated from blood with anti-CD-146 coated Dynabeads™. von Willebrand factor (vWF), CD 31 and UEA-1 staining were performed concurrently; tissue factor immunocytochemistry and assays for markers of apoptosis and necrosis were also carried out.

Results: Few circulating endothelial cells were seen in healthy controls (0-20, median 6 cells/ml) and patients with non-ANCA glomerulonephritis (0-21, median 4 cells/ml). Large numbers of circulating endothelial cells were detected in patients with active disease (20-5700 cells/ml, median 136 cells/ml, $p < 0.0001$ compared to healthy controls). Cell numbers fell considerably during successful immunosuppressive treatment. Patients in remission had moderately elevated cell numbers (0-52, median 16 cells/ml). There was a significant correlation between cell numbers and BVAS when all patients with quiescent and active vasculitis were included (Spearman rank correlation, $R=0.68$, 95% confidence interval 0.54-0.78, $p < 0.0001$, $n=78$). The vast majority of cells stained annexin/propidium iodide and tissue factor positive, indicating a necrotic and procoagulant phenotype.

Interpretation: The number of endothelial cells in peripheral blood is a novel marker of ANCA-associated small-vessel vasculitis; moreover, it is conceivable that these necrotic cells elicit an inflammatory response in their own right. Hence, our findings not only yield a new diagnostic tool but may also have considerable pathogenetic importance.

23-051

DIFFUSE ENDOTHELIAL DYSFUNCTION IS A COMMON FEATURE OF SNV

Bacon PA, Stevens RJ, Carruthers DM, Diler AD, Raza K, Townend J. University of Birmingham, Birmingham, UK.

Systemic vasculitis (SNV) centers around active inflammation in the wall of blood vessels, but the role of the lining endothelial cells has received little attention in assessment of the longer-term outcome. Our preliminary finding of endothelial cell dysfunction (ECD) in SNV (Raza K et al, *Circulation* 2000; 102:1470-1472) raised several questions about its significance, which we address here using two well-established tests of EC-dependent vasodilatation in a series of studies. Brachial artery (BA) function was tested by flow-mediated responses whilst skin microcirculation was assessed by iontophoresis of ACh, with appropriate positive controls for smooth muscle responses to nitrate, in a total of 58 patients.

(1) The occurrence of ECD at the BA was confirmed in 54 SNV patients ($p<0.001$ compared to matched controls). (2) This larger series allowed us to ask whether ECD was syndrome specific. In fact, significant ECD was found in ANCA-related small-vessel vasculitis (WG, MPA, and CSS) as well as cPAN affecting medium arteries. This implies that EC dysfunction in SNV is not restricted to vessels involved in the site of active inflammation. (3) To confirm this, we assessed microcirculation responses in clinically uninvolved skin. These were also significantly depressed in 36 cases of SNV ($p<0.0002$ compared to controls) and again involved both WG and cPAN. (4) To examine the mechanism we first focused on ANCA, which are involved in EC activation and injury. However, ECD did not correlate with either ANCA status or the diagnosis of an ANCA-related vasculitis. Renal involvement was not a significant correlate either. (5) Finally, we asked whether this diffuse ECD represented fixed damage by examining the effects of active therapy. TNF blockade with infliximab in four cases produced significant early improvement, maximum at 48 hours but reverting to baseline by 2 weeks. By contrast, steroid/cyclo pulses did not induce significant short-term changes but were associated with major normalization of EC function over 4/12.

These studies established that diffuse endothelial dysfunction occurs commonly in SNV but is potentially reversible, with important implications for future therapy. The relationship to clinical relapse and the responses to other therapy are under study. Finally, since similar ECD is seen in atherosclerosis, these studies predict an increased risk of cardiovascular events as a late sequel to SNV.