# Neutrophil-mediated mechanisms in non-vascular Behçet's syndrome

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## Abstract

Objective: Behçet's syndrome (BS) is a systemic vasculitis with several clinical manifestations. Neutrophils hyperactivation mediates vascular BS involvement, via a massive production of reactive oxygen species (ROS) and the release of neutrophil extracellular traps (NETs). We investigated neutrophil-mediated mechanisms of damage in non-vascular BS manifestations and explored in vitro the effects of colchicine in counteracting these mechanisms. Methods: NETs and intracellular ROS production was assessed in blood samples from 80 BS patients (46 with active non-vascular BS, 34 with inactive disease) and 80 healthy controls. Moreover, isolated neutrophils were incubated for 1 hour with an oxidating agent (2,2'-azobis (2-amidinopropane) dihydrochloride; 250nM), and the ability of pure colchicine pre-treatment (100ng/ml) to counteract oxidation-induced damage was assessed. Results: Patients with active non-vascular BS had remarkably increased NET levels [21.2 (IQR 18.3-25.9) mU/ml] compared to patients with inactive disease [16.8 (13.3-20.2) mU/ml] and to controls [7.1 (5.1-8.7) mU/ml], $p<0.001$]. Also, intracellular ROS tended to be increased in active BS, although not significantly. In active non-vascular BS, NETs correlated with neutrophils ROS production ($p<0.001$) and were particularly increased in patients with active mucosal ($p<0.001$), articular ($p=0.004$), and gastrointestinal symptoms ($p=0.006$). On isolated neutrophils, colchicine significantly reduced oxidation-induced NET production and cell apoptosis, though not via an antioxidant activity. Conclusion: Neutrophil-mediated mechanisms might be directly involved in non-vascular BS, and NETs, more than ROS, might drive the pathogenesis of mucosal, articular and intestinal manifestations. Colchicine might be effective to counteract neutrophils-mediated damage in BS, although further studies are needed.

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