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THE ASSOCIATION OF GLOBAL HEMOSTASIS MARKERS WITH THE RISK OF NEW DIGITAL ULCER ONSET-CIRCULATING EXTRACELLULAR VESICLES AS A PREDICTIVE MARKER OF INTERSTITIAL LUNG DISEASE PROGRESSION IN SYSTEMIC SCLEROSIS: A PROSPECTIVE COHORT STUDY

POVEZANOST GLOBALNIH BILJEGA HEMOSTAZE S RIZIKOM NASTUPA NOVIH DIGITALNIH ULCERACIJA - CIRKULIRAJUĆE IZVANSTANIČNE VEZIKULE KAO PREDIKTIVNI BILJEZI PROGRESIJE INTERSTICIJSKE BOLESTI PLUĆA U SISTEMSKOJ SKLEROZI: PROSPEKTIVNO KOHORTNO ISTRAŽIVANJE

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Introduction: Digital ulcers (DU) are associated with a high rate of morbidity and mortality and may be recurrent. Although vasculopathy is related to impaired hemostasis, its role in recurrent DU onset remains elusive. Interstitial lung disease (ILD) presents a leading cause of mortality in SSc, and a progressive pattern could be seen in around 30% of cases. The association between EVs and progressive ILD (pILD) was not previously investigated.
Methods: I. Markers of endothelial dysfunction, thrombin generation, overall hemostatic potential, and fibrin clot turbidity in plasma from 58 patients with SSc 46 matched healthy controls (HCs) were studied. Fibrin structure was visualized using scanning electron microscopy (SEM). 39 patients with a history of DUs were followed for 1.5 years, and the predictive value of all investigated markers for new DU onset was explored. II. Phosphatidylserine-positive EVs were analysed with flow cytometry and labelled as endothelial EVs (EEVs), platelet EVs (PEVs), leucocyte EVs (LEVs), EVs expressing ICAM1, TF and HMGB1. The serum levels of ICAM1, VEGF, and IL6 were measured by ELISA. Lung functional tests were done every 6–12 months over a 3-year follow-up period (FUP). Progressive ILD (pILD) was defined by the decline of FVC % from the baseline ≥10%, or 5–9%, along with a DLCO % decline of >15%.
Results: Over an FUP, 20/39 patients developed new DUs. CLT was prolonged ($P < 0.001$) in cases with new DU episodes, especially those with recurrent DUs. CLT was an independent predictor of new DUs (OR 1.2,95% CI 1.1–1.3). Over a FUP, 12/32 ILD cases developed a pILD, of which 58% had early dSSc and were immunosuppressive therapy naive. All analysed EVs, IL6, and VEGF levels were elevated in the pILD ($p<0.05$). Ml Cox R, controlling for VEGF and IL6, confirmed the independent association of ICAM1±EVs (HR 1.1, 95% CI 1.01–1.1) with pILD.
Conclusions: Impaired fibrinolysis might have an emerging role in underlying digital vasculopathy and its progression in SSc. Different circulating EVs play a role in SSc ILD and pILD. ICAM1±EVs could be a novel predictive biomarker of SSc-ILD progression, identifying cases that would potentially benefit from early aggressive treatment.

Keywords: systemic sclerosis, digital ulcers, lung disease, clot lysis time, extracellular vesicles
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