

A138 **EXCESSIVE FMS-LIKE TYROSINE KINASE3-LIGAND HERALDS LYMPHOMA IN PRIMARY SJÖGREN'S SYNDROME**

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Background and objectives To determine if the FMS-like tyrosine kinase 3 ligand (FL), a cytokine implicated not only in B cell ontogenesis and proliferation, but also in haematological malignancies, contributes to increases in the blood Bm2 and Bm2' B cell subsets and heralds lymphoma in patients with primary Sjögren's syndrome (pSS).

Patients and methods Serum levels of FL were measured in 64 pSS patients and 20 matched healthy controls (HCs). The densities of FL and its receptor Flt3 were determined in blood B cells and salivary gland (SG) samples by immunofluorescence. The effect of FL on B lymphocytes was then investigated by coculture with human SG (HSG) cell line cells. Finally, FL serum levels were measured in 334 patients from the French cohort of primary SS patients ('Assessment of Systemic Signs and Evolution of Sjögren's Syndrome', ASSESS). We evaluated the association between FL levels and lymphoma development (past or present), and disease activity according to the EULAR SS Disease Activity Index (ESSDAI).

Results Serum levels of FL were increased in patients with pSS, compared to HCs (135.8 ± 5.5 vs 64.4 ± 4.5 pg/ml, $p < 0.001$). These levels of FL correlated with the numbers of Bm2 and Bm2' ($r = 0.459$, $p < 0.0006$) in pSS patients, and Flt3 was selectively expressed in Bm2 and Bm2' cells. B cell culture experiments showed that FL potentiates the proliferative effect of anti-IgM stimulation. SGs-infiltrating B cells expressed Flt3, and epithelial cells produced FL. Thus, excesses FL appeared to be associated with high ESSDAI ($p < 0.05$) and lymphoma ($p < 0.0001$) in the 334 patients of the ASSESS cohort. ROC analysis showed that 175 pg/ml was the ideal cut-off to detect the association with lymphoma with the sensitivity 44% and the specificity 97.5%.

Conclusions Serum levels of FL are elevated in pSS, accompanied by abnormal B cell distribution, and associated with history of lymphoma. Flt3 is mainly expressed by Bm2 and Bm2' cells. Serum levels of FL might explain the clinical evolution of pSS to B cell lymphoma, thus opening new avenues for therapy.