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Fibrosis in Lymphoid Tissue is Associated with Peripheral Blood Regulatory T Cells

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Background

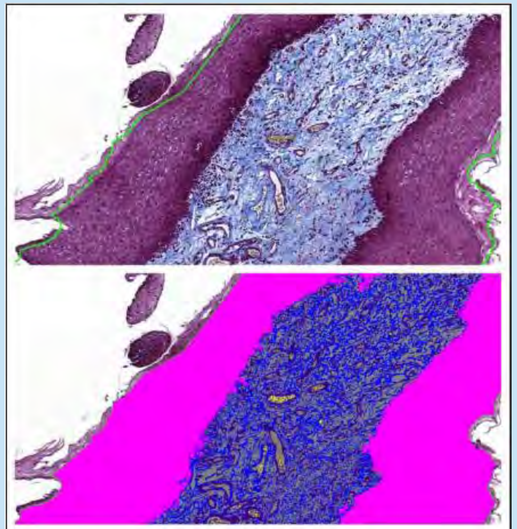
HIV may damage the structure in lymphoid tissue replacing the functional space with collagen. Regulatory T cells (Tregs) have anti-inflammatory properties exerting their function in part by secretion of transforming growth factor beta (TGF-b) which is known to induce fibrosis. In pathogenic SIV infection tissue fibrosis induced by TGF-b1-postive Tregs has been demonstrated. Thus, Tregs may participate in the pathogenesis leading to fibrosis in lymphoid tissue in HIV infection as well. We hypothesized that lymphoid tissue fibrosis was associated with percentage of peripheral blood Tregs and the level of immune activation.

Methods

Tonsil biopsies from 27 HIV-infected patients were examined. All patients had been on cART for a minimum of two years, had CD4 nadir <250 cells/µL, and HIV RNA had been ≤20 copies/mL for at least two years prior to inclusion in the study. Automated image analysis of tricrome-stained, paraffin-embedded tonsil biopsies determined the amount of fibrosis where $A_{fibrosis}$ was the area of fibrous connective tissue and A_{lesion} the area of the lesion including all tissue elements except epithelia, large lymphocyte clusters, and erythrocytes (see figure).Based on fibrosis index patients were divided into two groups with low fibrosis (n=13) and high fibrosis (n=14). Tregs (CD4+CD25+CD127^{low}FoxP3+) and activated cells (CD4+CD38+HLA-DR+) were determined in peripheral blood using flow cytometry. Differences between groups were analysed using Mann-Whitney U-test. Results are given as median (IQR).

Results

The groups of patients with low fibrosis vs. high fibrosis were similar in regard to age, sex, current CD4 and CD8 cell counts, and CD4 nadir. The group with low fibrosis displayed lower percentage of Tregs compared to the group with high fibrosis (4.8% (4.4-6.9) vs. 6.9% (5.6-8.4), P=0.0186). This was accompanied by lower percentage activated CD4+ cells in low fibrosis vs. high fibrosis (1.5% (1.0-2.2) vs. 2.5% (1.8-4.2), P=0.0319).



Masson tricrome-stained tonsil biopsy and result of automated image analysis. Blue:Fibrous connective tissue; Pink: epithelia; yellow: erythrocytes; purple/grey: other tissue components.

Clinical characteristics

Study population

Sex (males/total)	**25/27**
Age, years	**45** (39-55)
CD4 cell count, cells/µL	**390** (250-590)
CD8 cell count, cells/µL	**770** (630-920)
CD4 nadir (cellsµL)	**93** (26-185)

Data are given as median and (interquartile) ranges.

Conclusion

Patients with low amount of fibrosis in tonsil tissue also exhibited low percentage Tregs and immune activation, suggesting Tregs to be involved in the pathogenesis of fibrosis in HIV-infected patients on cART