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**Immune dysfunction in primary lymphoedema**

**Introduction**: Primary lymphoedema syndromes have a major impact upon quality of life and management is challenging. They frequently have a genetic basis, either hereditary or post-zygotic, in which case mutations are limited to the affected tissues. Systemic involvement may present with pleural and pericardial effusions and intestinal lymphangiectasia. One of the main functions of the lymphatic system is to enable immune cell trafficking and lymphoedema can therefore have a direct impact on immune homeostasis. Our aim is to understand how immune cell behaviour is affected by disruption to lymph pathways, and how different lymphoedema phenotypes influence patient immunology.

**Methods**: Blood samples were obtained from 146 patients diagnosed with a primary lymphoedema syndrome, who attended outpatient appointments within our centre. Two major phenotypic categories were compared, based upon whether systemic involvement was a recognised feature of a lymphoedema syndrome (‘systemic’) or not (‘simplex’). Samples were analysed for total lymphocyte counts, lymphocyte subsets (including CD4 and CD8 absolute counts) and immunoglobulin levels.

**Results**: Patients within the ‘systemic’ category were found to have a significantly lower total lymphocyte count (mean 1.30 vs. 2.17 x109/L, p<0.001), CD4 absolute count (mean 0.57 vs. 0.95 x109/L, p<0.001), CD8 absolute count (mean 0.65 vs. 0.82 x109/L, p=0.001) IgG level (mean 8.67 vs. 11.08 g/L, p<0.001), IgM level (mean 0.91 vs. 1.15 g/L, p=0.009) and IgA level (mean 1.25 vs. 1.68 g/L, p=0.008) compared to patients within the ‘simplex’ category. The presence of genital lymphoedema, irrespective of other phenotypic features, was also found to predict a significantly lower mean CD4 absolute count (p<0.001).

**Conclusion**: This study demonstrates that impaired lymph drainage in forms of primary lymphoedema syndromes can have a significant impact in the numbers and proportion of circulating lymphocytes, with particular targeting of CD4. Degrees of immunodeficiency may develop for reasons of impaired, and perhaps undetected, lymphatic failure. In some patients, CD4 levels were below 200 cells/mm3, which in other contexts, such as HIV infection, would be associated with systemic opportunistic infections. Patients with lymphoedema do not seem to contract more opportunistic infections despite this relative immunodeficiency, but can suffer with recurrent, often refractory cellulitis and recalcitrant viral warts. Further elucidation of the mechanisms and implications of these marked immunological abnormalities may contribute to reducing the burden of disease in affected patients.

**Reference**:
1. Gordon K, Varney R, Keeley V*, et al.* Update and audit of the St George’s classification algorithm of primary lymphatic anomalies: a clinical and molecular approach to diagnosis. *Journal of Medical Genetics*2020;**57:**653-659.