# Lymph node IL-18 expression in adult-onset Still's disease

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# Lymph node IL-18 expression in adult-onset Still's disease

IL-18 is a pleiotropic immunoregulatory cytokine that has been described and implicated in the pathogenesis of a variety of inflammatory diseases.[1–4]

Studies in murine models of arthritis and clinical studies suggest that dendritic cells, macrophages and synoviocites within the synovial membrane can produce IL-18.[1 5–7] IL-18 expression has in turn been implicated in the reciprocal regulation of other pro-inflammatory cytokines, such as tumour necrosis factor alpha.[8]

Recent data clearly demonstrated that IL-18 serum levels were significantly elevated in adult-onset Still's disease (AOSD) and correlated with disease activity and serum ferritin levels.[2–4] AOSD is characterised by substantial and dysregulated cytokine production, with higher levels of IL-18 messenger RNA expression detected in skin and synovial membrane biopsies of active AOSD compared with controls.[9]

However, the main source of IL-18 expression is as yet poorly understood.

We had the opportunity to investigate the expression of IL-18 in two lymph nodes of AOSD and thereby define this site as a critical tissue of origin for IL-18 hyperproduction. The expression was compared with non-specific lymphadenitis (NSL; no systemic inflammatory disorder present) and two lymph nodes from "normal" controls obtained during vascular surgery. Local IL-18 expression was analysed by immunohistochemistry using an IL-18 monoclonal antibody (clone 2D3B6; MD Biosciences, Switzerland) as previously described.[10] Greater expression of IL-18 was observed in AOSD lymph nodes compared with NSL and normal lymph nodes (fig 1). IL-18 was particularly overexpressed in hyperplastic, dysmorphic germinal centres detected in AOSD-derived tissue (fig 1E). Commensurate with our previous observations, IL-18 was also detected in germinal centres of mature follicles in NSL.[10] Of interest, whereas IL-18 was scarcely detected in the mantle zone in normal lymph nodes (fig 1A), high levels of expression were observed in the mantle zone of AOSD follicles (fig 1E). In addition, numerous

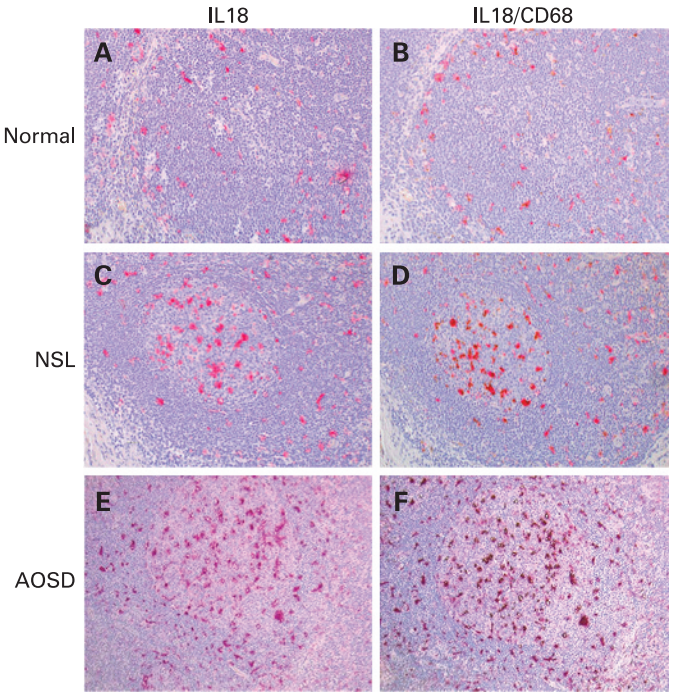


**Figure 1** IL-18 immunostaining (purple, left column) and double IL-18 (purple)/CD68 (brown, right column). Immunostaining within lymph nodes in non-reactive (A, B), reactive (C, D) and adult-onset Still's disease (AOSD) (E, F) lymphoid follicles. Original magnification 100×. IL-18 expression is massively upregulated within a hyperreactive dysmorphic germinal centre and in the mantle zone of the AOSD lymph node (E). In comparison, a secondary follicle in a normal lymph node shows strong, although lower, expression of IL-18 within the germinal centre and few positive cells in the mantle zone (C). Finally, IL-18 is expressed by scattered cells within a primary follicle (A). In all cases, double immunohistochemistry with CD68 clearly shows co-localisation with CD68-positive cells with dendritic cell/macrophage morphology. NSL, non-specific lymphadenitis.

IL-18-producing cells were observed in afferent lymphatics in biopsies obtained from AOSD and NSL patients compared with normal controls. Finally, we performed double immunohistochemistry for IL-18 and CD68, and found that IL-18 co-localised

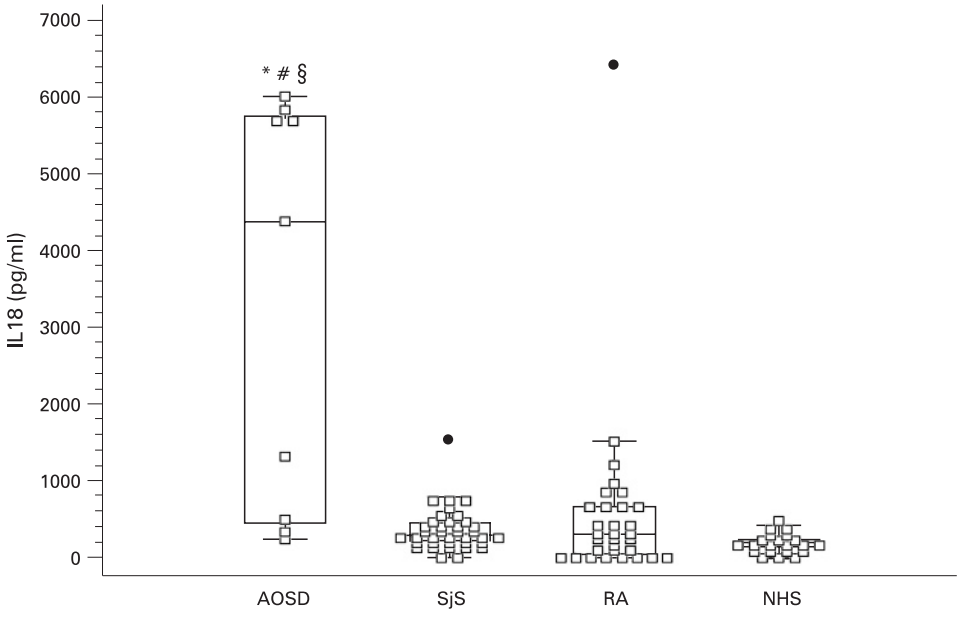


**Figure 2** Serum levels of IL-18 were measured by ELISA (R&D Systems, Minneapolis, MN, USA) as previously described. Box-and-whisker plot of IL-18 serum levels in adult-onset Still's disease (AOSD) patients (n = 9) (two men, seven women, mean age 28.8 years, range 14–56), primary Sjögren's Syndrome (SjS) patients (n = 37), patients with rheumatoid arthritis (RA) (n = 33) and normal controls (NHS) (n = 21). Median, quartiles, range and possibly extreme values are shown. *AOSD versus SjS: p = 0.001; #AOSD versus RA: p = 0.03; §AOSD versus NHS: p = 0.001.

almost exclusively with CD68-positive cells (fig 1F), indicative of a monocyte–macrophage lineage origin in lymph nodes.

We next confirmed increased serum IL-18 levels in nine cases of AOSD compared with patients with rheumatoid arthritis, primary Sjögren's syndrome and healthy subjects, as previously described (fig 2).[10] Moreover, IL-18 serum levels in AOSD patients correlated with serum ferritin levels (data not shown).

Although the importance of systemic IL-18 upregulation in AOSD is well documented, no data were previously available regarding the nodal expression of IL-18. We provide evidence that IL-18 is highly expressed at the protein level in the germinal centres and in the mantle zone of AOSD lymph nodes compared with non-specific lymphadenitis and ''normal'' lymph nodes as controls.

The increased systemic production of IL-18, observed in AOSD patients, could reflect the high local expression of this cytokine in the lymph node as an important site for such activation. This observation now needs to be confirmed in larger groups of patients to validate the hypothesis that the lymph node represents a major source of IL-18 in AOSD.

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# Axial bone proliferation causing cervical myelopathy in the mutilans form of psoriatic arthritis despite peripheral bone erosion

The radiographic features of psoriatic arthritis (PsA) can be broadly grouped into destructive and proliferative changes.[1] Arthritis mutilans, described by Moll and Wright[2] as ''digital telescoping resulting from severe osteolysis'' is the most florid form of erosive disease and occurs in less than 5% of cases. Bony proliferation is also characteristic of PsA and may help differentiate this condition from rheumatoid arthritis. We report a patient with PsA who developed cervical myelopathy as a result of proliferative bony change within the cervical spine, despite extremely severe erosive change at the peripheral joints.

The patient, a 65-year-old man, developed psoriasis at the age of 13 years and arthritis when he was 30 years old. His joint disease was resistant to medical therapy (non-steroidal anti-inflammatory drugs, intramuscular gold, sulphasalazine and methotrexate) and continued to progress. *x* Rays revealed extensive erosive change at the wrists and small joints of the hands and feet, with pencil-in-cup deformities at most of the proximal interphalangeal joints and bone lysis causing 30–50% resorption of proximal and middle phalanges at all digits of the hands except the left thumb.

He recently presented with numbness and tingling in the hands, exacerbated by coughing and associated with weakness. There was a history of neck stiffness and pain for several years. On examination, upper motor neurone signs were elicited in the upper and lower limbs, with brisk reflexes and upgoing plantar responses, suggesting cervical cord compression. Plain cervical radiography showed no instability at the atlantoaxial joint on flexion and extension views. Magnetic resonance imaging of the cervical spine showed multilevel disc disease, with disc bars and bulging of the ligamentum flavum at C2/3 and C3/4 causing spinal canal stenosis with T2w hyperintensity at this level indicating myelopathy. Extensive bone proliferation was noted around the odontoid peg and anterior arch of atlas. On multidetector computerised tomography scanning, bony bridging was demonstrated at the atlantoaxial joint and the occipito-atlantal junction (fig 1A,C,D), fixing the base of the skull to the upper spine.