A rare case of idiopathic multicentric Castleman disease in a patient with long-standing systemic autoimmunity

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This is an electronic version of an article published in:
https://doi.org/10.1080/03009742.2021.1947591

Original publication available at:
https://doi.org/10.1080/03009742.2021.1947591
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**Type of article:** Letter

**Title:** A rare case of idiopathic multicentric Castleman disease in a patient with long-standing systemic autoimmunity

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**Word count:** 821
LETTER (Case report)

Lymphadenopathy is a common manifestation of active rheumatic disease although other causalities, such as infections and malignancies, always need to be taken into account. For rheumatic diseases, this is particularly challenging since the risk of lymphoma is increased (1). Castleman disease (CD), occasionally seen in autoimmune diseases, is a rare non-malignant lymphoproliferative disorder, with an estimated incidence of 5–16 cases per million person-years (2–5). Radiologically, CD is differentiated in unicentric or multicentric lymphadenopathy (6). Histologically, CD is divided in hyaline-vascular, plasma cell and mixed subtypes (7, 8). The histology of idiopathic multicentric CD (iMCD) often displays a mixed hyalin-vascular and plasma cell subtype (7). In this letter, we describe an unusual case of long-standing rheumatic disease with late onset of iMCD.

A Caucasian woman, born in 1970, was diagnosed with rheumatoid arthritis in the mid-90’s at our unit based on symmetric non-erosive polyarthritis, positive rheumatoid factor and hypergammaglobulinemia (26 g/L). Subsequently, she developed Raynaud’s phenomena and sicca symptoms. Hyposalivation was confirmed and keratoconjunctivitis sicca diagnosed by the ophthalmologist. Positive ANA with speckled pattern combined with Ro/SSA- and La/SSB-antibodies led to a diagnostic reevaluation with change to primary Sjögren’s syndrome in 2001. Later, the patient developed recurrent episodes of fever (38–39°C), leukopenia and systemic inflammation reflected by elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) but no signs of hypocomplementemia or antiphospholipid antibodies (aPL). Treatment primarily included corticosteroids and hydroxychloroquine (HCQ), but due to side-effects the latter was switched to methotrexate. However, methotrexate was discontinued in 2004 due to transaminasemia and only low doses of corticosteroids were occasionally used to handle the recurrent attacks of fever and arthritis.

New symptoms (e.g. malar rash, photosensitivity and thrombocytopenia) emerged during 2008–2010. In 2012, a dermatologist judged the extensive skin rash located over hands and feet as compatible with lupus. HCQ was again initiated, but without significant effects on the cutaneous manifestations and cytopenia. A positive Coombs’ test in the absence of hemolysis, combined with elevation of immunoglobulin isotypes (IgG, IgM, IgA), was recorded but without hypocomplementemia and aPL. She complained of recurrent pleuritic chest pain, although evident signs of serositis on chest X-ray or echocardiography could not be shown.
In 2019, the patient experienced severe attacks of abdominal pain, diarrhea and fever combined with a platelet count of <20x10^9/L. ESR and CRP were high, but procalcitonin and feces-calprotectin were within reference. Hypoalbuminemia without proteinuria and preserved renal function were observed and liver enzymes were normal. CT showed moderate splenomegal and lymphadenopathy in the hepatic hilum and para-aortic region, but no other pathology. However, as lymph nodes were ≤1.5 cm, the decision was made to refrain from biopsy. Prednisolone 60 mg daily were given, but platelet count remained low. Recurrent fever, fatigue, night sweats and thrombocytopenia along with the tapering of corticosteroids led to the decision to initiate rituximab (RTX) in November 2019 (1000 mg times two). RTX-infusion was repeated 6 months later and gave some effect on platelet count, whereas other symptoms did not respond.

A new CT, performed during another episode of abdominal pain, dyspnea and fever, showed progression of lymphadenopathy in para-aortic, para-iliac and both axillary regions. Raised ESR/CRP along with slightly elevated lactate dehydrogenase and β-2-microglobulin were observed. A broad malignancy investigation, including endoscopic examinations, was performed without any pathological findings. A lymph node biopsy from axillary region displayed no signs of non-Hodgkin’s lymphoma (including flow cytometry assessment). Instead, the histopathological findings were typical of CD with presence of numerous plasma cells (whereof some were IgG4-positive), atrophic germinal center with hyalinization of the vessel walls and expanded Mantle zones showing ‘onion skin’ appearance (**Figure 1**). No prominent germinal centers or necrosis were identified. Another axillary lymph node biopsy taken 6 months later showed similar histopathology. A PET-scan confirmed multicentric distribution of lymphadenopathy; the largest lymph node measured 2 cm in short-axis diameter (**Figure 2**).

Herpes viruses (Epstein-Barr, CMV, HH-6, HH-8) were assessed with quantitative PCR with negative results. Tuberculosis was excluded with interferon-γ-release assay. Plasma IgG4 was controlled twice; one borderline result (2.1 g/L; reference <1.3) and later negative. Plasma IL-6 was above reference in three consecutive tests.

This woman with a 25-year history of Sjögren-like lupus developed abdominal lymphadenopathy, irresponsible to antirheumatic therapy, combined with constitutional
symptoms, hypergammaglobulinemia and severe cytopenia. Extensive investigation was necessary to exclude malignancy (particularly lymphoma), but the case illustrates that also non-malignant lymphoproliferative disorders should be considered. The diagnosis was facilitated by radiology demonstrating multiple enlarged lymph nodes combined with typical histopathology (major criteria). Additional clinical and laboratory findings (minor criteria) were also met to satisfy the diagnostic international consensus criteria for iMCD (8–10). In line with the international, evidence-based consensus treatment guidelines for iMCD, IL-6 inhibition has been initiated (10). The patient has received a first infusion of tocilizumab without side-effects, and further infusions are planned for every fourth week. The plan is further to evaluate the efficacy of tocilizumab with a new PET-scan within 6–12 months.
Figure Legends

Figure 1: Castleman disease-like histology in the extirpated lymph nodes from the right axil. (A) Lymph node measuring 13.7 mm in diameter and showing atrophic germinal centers. (B) Germinal center with concentric ring formation composed of small lymphocytes, giving the appearance of “onion skin”. (C) Occasionally, paracortical vessels (arrow) radially penetrate germinal centers, forming lesions that resemble a lollipop. Some fibrosis is also seen. (D) Extensive vascular hyalinization (arrows) was present. The scale bar corresponds to 2 mm in (A) and 0.05 mm in (B–D).

Figure 2: The figure demonstrates positron emission tomography (PET) scans in whole body (A) and abdominal (B) sections showing marked enlarged lymph nodes in retroperitoneal and fossa supraclavicularis regions with evident fluorine-18 fluorodeoxyglucose ($^{18}$F-FDG) radioisotope captation.
References
