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Reactive lymphadenopathy with concurrent idiopathic plasma cell variant Castleman disease, amyloid deposition and non-caseating granulomas

Sir,

Amyloid lymphadenopathy is characterised histologically by effacement of the nodal architecture by eosinophilic amorphous material that exhibits apple-green birefringence with Congo red stain examined in cross-polarised light. The pattern of effacement can be diffuse, involve follicles predominantly (i.e., follicular), or a combination of follicular and diffuse. Immunoglobulin-derived light chain amyloidosis (AL amyloid) is most common. A recent report of 47 cases found that 39 were systemic and four localised AL amyloid, whereas only one case each was AA (serum amyloid A protein), wtTTR (wild type transthyretin), V122ITTR (transthyretin V122I).[1] The identification of AL amyloid is often suggestive of plasma cell dyscrasia, idiopathic amyloidosis or a lymphoproliferative neoplasm. AA amyloid, sometimes referred to as secondary amyloidosis, is often associated with reactive conditions including autoimmune diseases and infectious aetiologies.[2] Due to a persistent chronic inflammatory state, lymph nodes can be complicated by the deposition of serum amyloid A protein (SAA) and development of secondary amyloidosis. Here, we present a patient with lymphadenopathy attributable to idiopathic plasma cell variant Castleman disease, amyloid deposition, and non-caseating granulomas.

A 62-year-old human immunodeficiency virus (HIV)-negative African American woman presented with dysphagia and fatigue. She had a history of diabetes type II, hypothyroidism, Plummer−Vinson syndrome and persistent lymphadenopathy of the porta hepatis. Five years prior to this visit, the patient had a needle core biopsy of an enlarged portal lymph node that revealed scattered secondary follicles with an increased number of small mature-appearing plasma cells in the interfollicular areas. Some follicles showed small, lymphocyte-depleted germinal centres. No amyloid was identified. No aberrant B or T cells were identified by flow cytometry immunophenotypic analysis. Molecular studies using polymerase chain reaction (PCR)-based methods show no evidence of monoclonal *IGH* or *TRG* or *TRB* rearrangements. A diagnosis of plasma cell variant Castleman disease was suggested.

For the current visit, laboratory studies showed moderate microcytic anaemia with a haemoglobin level of 7.6 g/dL [reference range (RR) 12.0−16.0 g/dL] and MCV of 65 fl (RR 82−92 fl). In addition, increased free kappa (115 mg/L; RR 3.3−19.4 mg/L) and lambda light chain (78 mg/L; RR 5.7−26.3 mg/L) were present with a normal kappa/lambda ratio of 1.46 (RR 0.26−1.65). A computed tomography (CT) scan of the abdomen showed lymphadenopathy: a 2 cm supra-pancreatic lymph node, a 2 cm hepatic artery lymph node, and a 5 cm porta hepatis lymph node that were stable compared to the imaging studies performed 5 years previously. No other enlarged lymph nodes were identified. Foci of calcified granulomas were detected in the liver, spleen and right lung base. The patient underwent an excisional biopsy of portal and supra-pancreatic lymph nodes. Histological examination revealed enlarged lymph nodes with patent sinuses and variably sized follicles scattered in the cortex and medulla (Fig. 1A−D). Many follicles showed deposits of amorphous eosinophilic material in the centres of the follicles and some showed mantle zone hyperplasia with an 'onion-skin' appearance (Fig. 1E,F). The interfollicular regions and medulla were occupied by sheets of cytologically mature plasma cells. Vascular proliferation was present in the interfollicular areas and occasional hyalinised blood vessels penetrating follicles (hyaline-vascular lesions) were present (Fig. 1G,H). In addition, focal distinct non-caseating granulomas containing rare giant cells and asteroid bodies were present (Fig. 1K,L). Special stains were performed to characterise the eosinophilic deposits and non-caseating granulomas. Congo-red stain demonstrated apple-green birefringence in areas with eosinophilic deposits (Fig. 1I,J,M,N,O). AFB was negative for acid-fast bacilli and GMS was negative for fungal organisms. Immunohistochemistry (IHC) for IgG4 highlighted <10% of IgG+ plasma cells. HHV8 stain was negative. Flow cytometry analysis showed no aberrant B or T cells and polytypic plasma cells.

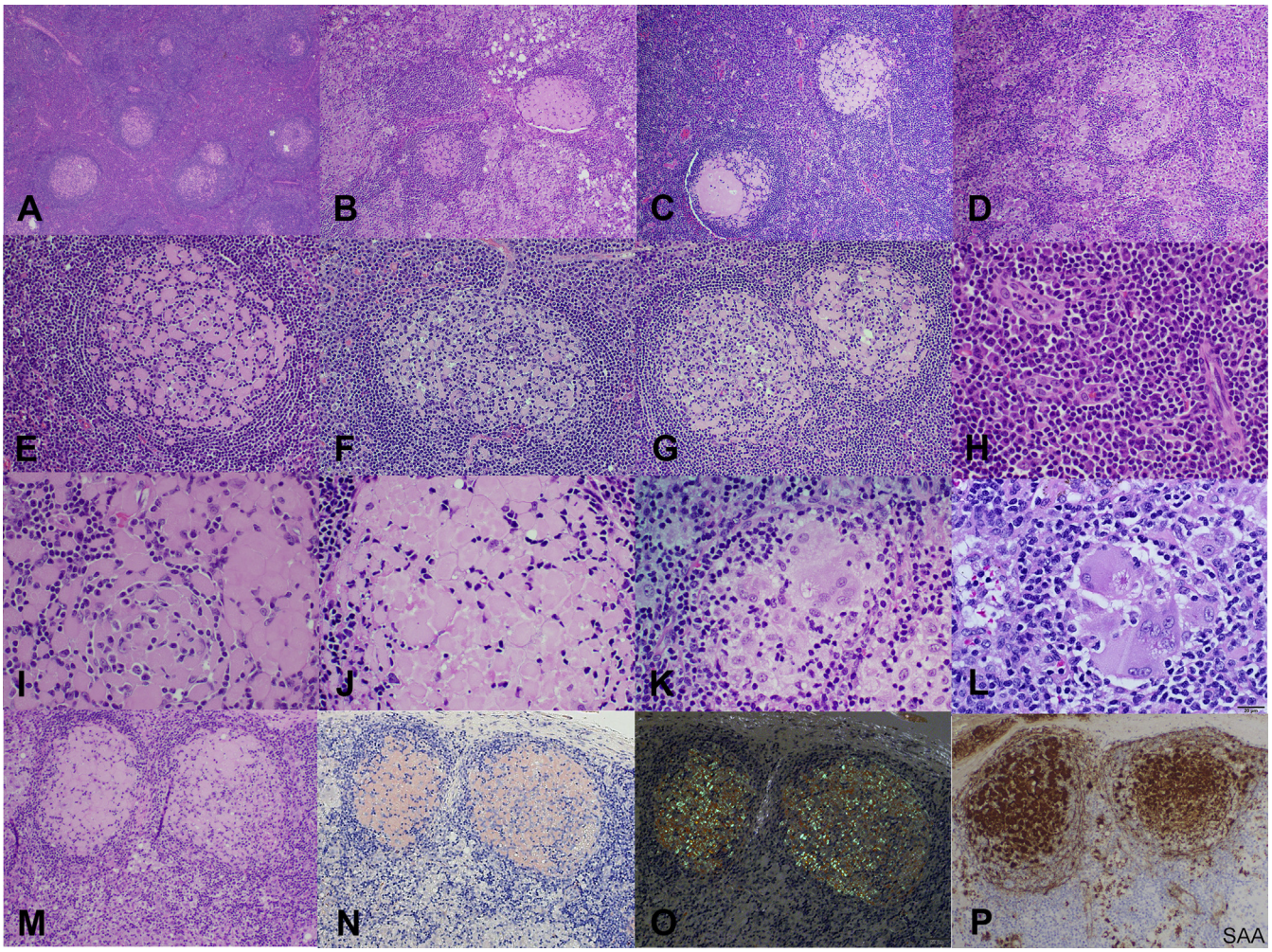

Fig. 1 The histopathological features of reactive lymphadenopathy with Castleman disease, amyloidosis and non-caseating granulomas. (A−D) Enlarged lymph nodes with variably sized follicles scattered in the cortex and medulla. (E,F,M) Many follicles with eosinophilic deposits in the follicle centres and some follicles with mantle zone hyperplasia. (G,H) Sheets of mature plasma cells and vascular proliferation present in the interfollicular areas. Occasional hyalinised vessels penetrating the follicles are also present. (K,L) Focal distinct non-caseating granulomas containing rare giant cells and asteroid bodies. (N,O) Congo-red stain with apple-green birefringence in areas with eosinophilic deposits. (P) The amyloid deposits are SAA positive.

In situ hybridisation showed polytypic plasma cells and rare small cells positive for EBV-encoded RNA (EBER). PCR analysis was negative for monoclonal *IGH* and *TRG/TRB* rearrangements.

In light of positive Congo red staining and absence of clonality in plasma cells, we performed IHC for serum amyloid A (SAA) protein and showed that the amyloid deposits were positive consistent with AA amyloidosis (Fig. 1P). Hence liquid chromatography tandem mass spectrometry (LC MS/MS) was performed for confirmation of the amyloid type. A peptide profile consistent with AA type amyloid was detected, supporting the diagnosis of secondary amyloidosis. The overall findings are consistent with HHV8-negative/idiopathic Castleman disease, plasma cell variant with concurrent AA type amyloidosis and non-caseating granulomas.

To the best of our knowledge, this case is the first report of concurrent idiopathic Castleman disease, amyloidosis and non-caseating granulomas.[3−7] Given the imaging findings (the presence of granulomas in lung, spleen and liver) and histological findings (non-caseating features with asteroid bodies, and negative for microorganisms), the non-caseating granulomas are most consistent with sarcoidosis. Sarcoidosis is a systemic inflammatory disorder of unknown aetiology. The association of sarcoidosis with lymphoproliferative disorders was first described in 1986 by Brincker *et al.* as 'sarcoidosis lymphoma syndrome' in which the granulomatous disease can antedate, follow or occur simultaneously with a haematological neoplasm;[8] this association remains controversial.

Castleman disease, a benign lymphoproliferative disorder, has been rarely reported to be concurrent with sarcoidosis. Interleukin-6 (IL-6) plays a critical role in Castleman disease and its variants. IL-6 is a cytokine released by haematological cells and fibroblasts with broad effects in multiple organs and systems, leading to a variety of clinical symptoms such as fever, fatigue, anaemia, and thrombocytosis. IL-6 also activates T cells and B cells to produce antibodies leading to hypergammaglobulinaemia and lymphoproliferative abnormalities. High IL-6 levels have been detected in the blood from patients with sarcoidosis and found to be actively involved in inflammation and development of non-caseating granulomas.[9] It seems reasonable to suggest that IL-6 could be the pathophysiologic link between these two disorders and therefore the coexistence of Castleman disease and sarcoidosis appears to be a non-random association.

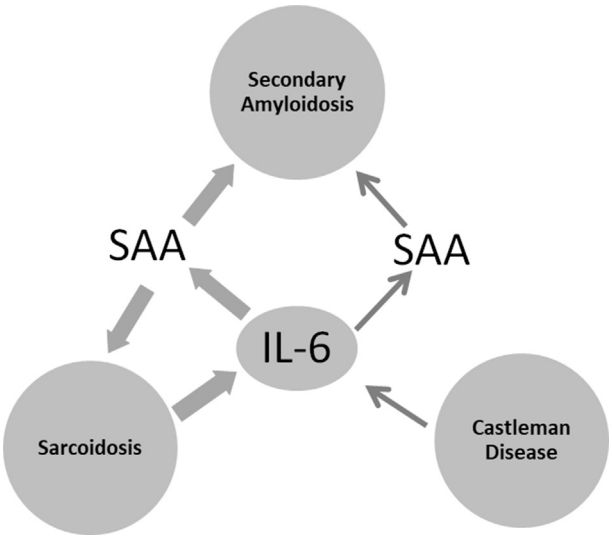

Fig. 2 The presumptive pathogenesis of reactive lymphadenopathy with concurrent Castleman disease, sarcoidosis and reactive amyloidosis. IL-6 might trigger persistent overproduction of SAA protein which may contribute to concomitant Castleman disease, sarcoidosis and secondary amyloidosis.

Secondary type AA amyloidosis is characterised by extracellular deposition of insoluble proteins which may impact the function of involved organs. AA amyloid deposition is known to complicate active chronic conditions seen in inflammatory diseases and malignancies. Serum amyloid A protein (SAA) is the precursor protein for reactive/secondary amyloidosis. One study indicated that SAA might be responsible for sarcoidosis.[10] In that study, the authors showed high levels of this protein in the granulomas of sarcoidosis and confirmed that SAA protein was the cause of sustained chronic inflammation of affected patients.[11] In the patient we report persistent chronic inflammatory disease as a result of Castleman disease and sarcoidosis, driving persistently elevated IL-6 levels, which might explain the overproduction of SAA protein leading to disease progression and manifestations of secondary reactive amyloidosis.[12] Given that SAA protein might have a pathogenic role in the granulomatous inflammation of sarcoidosis through a sustained inflammatory reaction, the possibility of increased SAA triggering sarcoidosis in this patient should be also considered (Fig. 2). Overall, SAA might contribute to concomitant Castleman disease, sarcoidosis and secondary amyloidosis.

In conclusion, Castleman disease can be rarely associated with sarcoidosis and secondary amyloidosis. Our report extends the literature by contributing a case of concurrent idiopathic Castleman disease, sarcoidosis, and amyloidosis. Dysregulation of the immune system, sustained chronic inflammation, and SAA protein may be the underlying aetiology of these concomitant disorders/diseases.

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TdT-positive high grade B-cell lymphoma transformed from grade 3B follicular lymphoma in an HIV-positive patient

Sir,

Follicular lymphoma (FL) is graded as low (grades 1 and 2) and high (grades 3A and 3B) based on the number of centroblasts.[1] Low grade FLs are known to be clinically indolent, but have a natural tendency to recur or transform into more aggressive and diffuse neoplasms, usually diffuse large B-cell lymphoma (DLBCL).[2] Grade 3B FL is thought a different entity from grade 1-3A FL because its molecular, cytogenetic and immunophenotypic features resemble, in part, cases of DLBCL.[3] While progression from lower to higher grade is common in FL, blastoid transformation is rare.[4]

Human immunodeficiency virus (HIV) infection is associated with a higher risk of lymphoma development. HIV-associated NHLs are a heterogenous group, but are predominantly aggressive B-cell lymphomas.[5] DLBCL and Burkitt lymphoma (BL) are the most common subtypes, whereas FLs and peripheral T-cell lymphomas are rarely associated with HIV infection.[6]