Case Report

Castleman’s disease with nephrotic syndrome, amyloidosis and autoimmune manifestations

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Introduction

Castleman’s disease (also called giant lymph-node hyperplasia or angiofollicular lymph-node hyperplasia) is a highly heterogeneous clinico-pathological entity belonging to the lymphoproliferative disorders. Originally described in 1956 by Castleman and co-workers [1] as a large, benign, unique asymptomatic mass of mediastinal lymph nodes, it was shown in subsequent reports to include extra-mediastinal and multicentric forms [2].

Two histological patterns of lymph nodes were described: the hyaline–vascular and plasma-cell types. The former is more common (80–90%), and is characterized by the proliferation of capillary vessels in germinal centres of lymphatic folliculi, which assume a hyaline aspect. It is classically reported to have mono-localization, often mediastinal, and a benign course after removal of the mass. The plasma-cell variant is less frequent (10–20%) and presents hyperplastic follicles interspersed by sheets of plasma cells. It is often multi-centric and usually associated with systemic manifestations of inflammatory disease. The prognosis is worse, with infections and progression to lymphoma as the major causes of death. Mixed or transitional forms have also been described [2].

We report here an unusual case of Castleman’s disease of the hyaline–vascular type with multi-centric localization (cervical, mediastinal, abdominal), characterized by nephrotic syndrome, systemic amyloidosis of the AA type, and a plethora of autoimmune manifestations: uveitis, deep venous thrombosis, anti-cardiolipin antibody positivity, pyoderma gangrenosum, epididymitis, and sacroiliitis.

Case

A 39-year-old male patient of Tunisian origin was admitted to our unit in 1999 because of abdominal pain, nephrotic syndrome, and latero-cervical lymphadenopathy.

The patient’s past medical history had begun 7 years earlier. In 1992, he sought medical attention for recurrent ulceration in the lower limbs. At that time a skin biopsy was performed in a dermatology unit and showed pyoderma gangrenosum.

Two years later (1994) he began reporting recurrent abdominal pain crises, and during one of these he underwent appendectomy (the results of the histological examination are not available). The operation was complicated by thrombosis of the inferior vena cava and did not provide any relief to the patient’s abdominal complaints. In the same year the patient noticed the appearance of a left latero-cervical mass, but no further investigations were undertaken.

From 1995 the patient’s clinical picture became complicated by uveitis, epididymitis, arthralgias, chronic lumbar back pain, recurrent diarrhea, proctorragia, weight loss (the exact chronology could not be documented by the patient), and led to his admission to a department of internal medicine (1997). On that occasion, proteinuria (2 g/day), and positivity for anti-cardiolipin IgG (52.8 U/ml) and anti-hepatitis C virus (HCV) antibodies (HCV-RNA was negative) were found. Multiple left latero-cervical lymph nodes were documented by ultrasound examination, in addition to the node that had been present since 1994, and was about 5 cm in diameter. The biopsy of a minor lymph node showed diffuse histiocytosis, focal
amyloid, and no granulomas. A bone marrow biopsy was normal. Chronic inflammatory bowel diseases were excluded by colonoscopy and small-bowel enema. The attending physicians diagnosed an anti-phospholipid antibody syndrome and the patient was treated with oral anticoagulants and corticosteroids. The latter were spontaneously withdrawn by the patient about 1 year later.

No history of chronic fever or familial amyloidosis was reported.

On admission to our unit (1999), the clinical picture was dominated by severe abdominal pain and overt nephrotic syndrome with normal renal function (proteinuria ranged from 3 to 7 g/day, with electrophoretic pattern of glomerular, partially selective proteinuria; proteinuria was 3.62 g/dl, albuminaemia 30.6%, and creatinine clearance 127 ml/min).

Physical examination showed orthostatic hypotension, 3+ pre-tibial pitting oedema, superficial cava–cava venous reticulum on the abdomen, a left latero-cervical mobile mass of about 5 cm, and skin dyschromia of the lower limbs. The abdomen had no signs of peritonitis.

The abdominal investigation by ultrasound and colour Doppler, computed tomography (CT) and angio-NMR confirmed the already identified inferior vena cava thrombosis, excluded other surgical pathology, and revealed multiple mesenteric and para-aortic-caval lymph nodes of approximately 1 cm in diameter. Another lymph node of about 1 cm was shown by thoracic CT at the right pulmonary hilus.

The laboratory showed normal white blood cell count (6300/μl), microcytic anaemia (haemoglobin 9.5 g/dl, mean cell volume 72 fl with normal haemoglobin electrophoresis), normal reticulocyte count (60 × 10⁶/l), reduced iron stores (serum iron 30 μg/dl, serum ferritin 25 μg/ml, total iron binding capacity 1.08 g/l), increased inflammatory indices (C-reactive protein 40 mg/l, erythrocyte sedimentation rate 64 mm/1st h, IL-6 23 pg/ml); normal liver enzymes, serum β₂ microglobulin (2.31 ng/l) and circulating angiotensin-converting enzyme levels (50 U/l). No monoclonal components were found in serum or urine. Serology for autoimmunity was negative (ANA, ENA, rheumatoid factor, anti ds-DNA, SS-A, SS-B, anti-Sm, anti-RNP, anti-Scl70 autoantibodies, C3, C4, immunoglobulin dosage, cryoglobulins, ANCA). In particular, positivity for antiphospholipid antibodies was not confirmed (lupus-like anticoagulant was negative, anti-cardiolipin IgG was 8 U/ml, anti-cardiolipin IgM was 3 U/ml).

Serology for infections was negative, including human immunodeficiency virus (HIV), and HCV (both HCV antibodies and HCV-RNA). IgG antibodies were positive only for cytomegalovirus (CMV), Epstein–Barr virus (EBV), and Toxoplasma. A PPD skin test was non-reactive. Tests for BK in the sputum and parasites in the stool were also negative.

The largest cervical mass of 5 cm was surgically removed and histological examination revealed Castleman’s disease of the hyaline–vascular type with focal deposits of amyloid (Figure 1). The patient underwent a renal biopsy, resulting in a diagnosis of amyloidosis with intense glomerular and interstitial vessel involvement. The potassium permanganate pre-treatment abolition of Congo red staining, the absence of κ and λ deposits on immunofluorescence, and the positive immunostaining with anti-human amyloid A component antibody (Dakopatts, Denmark) confirmed the diagnosis of renal amyloid of the AA secondary type (Figure 2), which was also found in multiple intestinal biopsies.

Because of the history of arthralgias and back pain, X-rays were performed on pelvis, spine, and main joints, and showed bilateral sacroiliitis.

The patient was treated with colchicine (1 mg/day), indomethacin (75 mg/day), diuretics, and a 2-month corticosteroid course (prednisone 1 mg/kg/day, which was later tapered off and stopped because of the occurrence of severe left lower-limb phlebitis).

Three months later, the patient’s general conditions were ameliorated, abdominal and back pain were reduced, nephrotic syndrome had partially remitted (proteinuria was 2.12 g/day, proteinuria 5.23 g/dl, and albuminaemia 38.8%), and inflammatory indices were reduced (C-reactive protein was 5 mg/l, and IL-6 12 pg/ml). Anaemia also had improved (haemoglobin 11.2 g/dl).

**Discussion**

Since its initial description, Castleman’s disease has been redefined from a localized tumour-like mass of lymphoid tissue, considered to be hamartomatous, to a systemic disease with general manifestations and multiple organ involvement. The localized forms are often mediastinal, asymptomatic, and associated with the hyaline–vascular histological pattern. Multicentric forms often have an aggressive and relapsing course,
and are usually associated with the plasma cell pattern and with systemic manifestations.

Our case is unusual in that the hyaline-vascular histological pattern was observed in a patient with documented multi-station lymph-node involvement (the major being cervical, the others mediastinal and abdominal) and an impressive concomitant chronic inflammatory state. In fact, beyond the general and previously described inflammatory signs (malaise, weight loss, anaemia, increased inflammatory indices), the patient’s clinical history was characterized by a plethora of autoimmune manifestations, including pyoderma gangrenosum, uveitis, epididymitis, sacroiliitis, and positive antcardiolipin antibodies (which were not re-confirmed, probably due to the previous corticosteroid treatment).

As currently understood, Castleman’s disease is considered to be a heterogeneous entity related to conditions of immune deregulation. In this respect, it is interesting that various disorders of the immune system may be characterized by Castleman-like histological changes, such as infections (HIV) and primary autoimmune diseases (systemic lupus erythematosus, POEMS syndrome, etc.) [2]. When this patient came under our observation, anti-HCV antibodies were no longer present (both HCV antibodies and HCV-RNA were negative) and other infections, including HIV, were ruled out. The autoantibody pattern and the clinical picture did not point to any primary autoimmune disease. Moreover, the cervical mass, from which Castleman’s disease was subsequently diagnosed, had appeared before many of the organ complications, reinforcing our hypothesis that Castleman’s disease was responsible for triggering the inflammatory response with consequent autoimmune organ manifestations and secondary AA-amyloid deposition, which in turn was responsible for the nephrotic syndrome, the gastrointestinal disorders, and orthostatic hypotension.

Systemic amyloidosis is a very rare complication of Castleman’s disease. Only 17 cases have been described, and only nine of these had nephrotic syndrome caused by documented renal amyloidosis [3]. All were of the plasma cell or mixed histological pattern. Other reported forms of renal involvement in Castleman’s disease are rare and heterogeneous, and include minimal-change disease, membranous GN, membranoproliferative GN, mesangial proliferative GN, and interstitial nephritis [4].

Recent studies have demonstrated an association of Castleman’s disease with excess production of the cytokine IL-6 [4]. IL-6 is a pleiotropic cytokine produced by several cell types, including activated monocytes, B cells, endothelial cells, fibroblasts, and mesangial cells. It has a panoply of biological effects, including a major regulatory effect on acute-phase response in humans. Large amounts of IL-6 were shown to be produced at the germinal centres of hyperplastic lymph nodes from patients with Castleman’s disease, and clinical improvement was observed along with decreases in IL-6 levels after the removal of the involved lymph nodes [4] or treatment with anti-IL-6 antibodies [5]. Corticosteroid therapy has also been shown to reduce IL-6 levels.

Accordingly, our patient had increased IL-6 levels (23 pg/ml) on admission to our unit. Three months after the excision of the largest lymph node mass and the initiation of therapy (steroids, colchicine, and indomethacin), IL-6 decreased to near normal values (12 pg/ml) and the clinical picture ameliorated (partial remission of the nephrotic syndrome, lessening of abdominal and back pain, improvement of anaemia, and reduction of inflammatory indices).

The treatment of Castleman’s disease and the possible reversal of both amyloidosis and the nephrotic syndrome are controversial issues, based essentially on case reports, since controlled clinical studies are lacking because of the rarity of the disease. In some reports on monocentric forms, it was shown that the surgical removal of the lymph node mass was curative [6,7] and led to the regression of the nephrotic syndrome and of amyloidosis, as detected by abdominal fat aspiration biopsy [6]. However, a recent report,
although confirming the regression of the nephrotic syndrome after excision of an abdominal lymph node, documented no regression of renal amyloid deposits 1 year after surgery [3]. Some reports documented no regression of the nephrotic syndrome after lymph-node excision [8,9], whereas some showed regression with colchicine therapy [9].

The management of multicentric Castleman’s disease is even more controversial. The surgical management did not provide any long-term benefits. However, partial resection of a large mass of involved tissue has been reported to produce transient symptomatic improvement in some patients, as it seems to have done in the present case. Current approaches include high-dose corticosteroids, and in some cases the addition of antineoplastic agents, with poor clinical benefits [10]. In addition to surgery, we decided to use high-dose corticosteroids and colchicine. This strategy, beyond reducing the lymphoid bulk by excision of the largest mass, was aimed at reducing the degree of immunostimulation. We added indomethacin for antalgic and anti-proteinuric effects. The 3-months follow-up showed that this strategy could achieve at least partial success.

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References


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