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CASE REPORT

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Secondary amyloidosis in Castleman's disease: review of the literature and report of a case

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Abstract It is quite rare to diagnose secondary amyloidosis during the course of Castleman's disease (CD). A 51-year-old female who complained of fatigue, weight loss, and fever was diagnosed with CD – plasma cell type – in our hospital in 1993. One year after diagnosis, she developed nephrotic syndrome, the etiology of which was found to be secondary amyloidosis based on renal biopsy. As the patient rejected therapy, she was discharged after only symptomatic treatment. At her last follow-up in March 2001, she had no complaints; physical examination, blood chemistries, and urinalysis were normal. Abdominopelvic tomography revealed no lymphadenopathy in the abdomen, which had been previously present. We could identify 17 other cases of CD with secondary amyloidosis in the literature. Ours is the 18th such case and the 2nd case of multicentric CD leading to amyloidosis. This case also shows that CD might sometimes run a relatively benign course being cured with no therapy, whereas it might have a rapidly fatal downhill course – even with therapy – in others. Still, effective treatment strategies need to be developed.

Keywords Castleman's disease · Nephrotic syndrome · Secondary amyloidosis

Introduction

Castleman's disease (CD) was first described in 1956 as a benign lymphoproliferative disease, mostly involving the mediastinum [1]. The etiology is not known with certainty, but thought to be infectious or inflammatory in origin [2]. In the review by Keller et al. [3], CD was divided into two histologic subtypes. The hyaline vascular (HV) subtype accounts for 91% of the cases and usually produces only a mass effect. The plasma cell variant is less common occurring in 9% of the cases and is often accompanied by systemic manifestations such as fever, anemia, thrombocytosis, hyperglobulinemia, increased erythrocyte sedimentation rate, splenomegaly, and peripheral lymphadenopathy [3].

Renal dysfunction in CD is heterogeneous and might induce an abnormal urine sediment, mild to moderate proteinuria, mild hematuria, or impaired renal function [4, 5, 6]. Nephrotic syndrome due to secondary amyloidosis (AA type) is quite a rare occurrence in CD. The treatment of amyloidosis secondary to CD is presently unknown. In unicentric disease, resection of the tumor mass might be effective [7, 8, 9]. However, the role of surgery in multicentric disease is limited, and the efficacy of systemic therapy, e.g., steroids, is uncertain [9]. In this report, we provide a brief review of published cases of CD with secondary amyloidosis, summarizing different treatment modalities used so far. In addition, we present a patient with CD who developed nephrotic syndrome secondary to amyloidosis and recovered without any surgical or medical therapy.

Case report

A 51-year-old female was referred to our hospital in 1993 with a 3-month history of fatigue, weight loss (8 kg in 3 months), and fever. Her past medical history and family history were not significant. Physical examination revealed conjunctival pallor. Blood pressure was 120/70 mmHg, heart rate 84 bpm, and temperature 38.4°C. There were 3 cm of hepatomegaly and 5 cm of splenomegaly. Left axillary, right inguinal, bilateral cervical, and supraclavicular lymphadenopathies were present.

Laboratory values were as follows: erythrocyte sedimentation rate (ESR) 126 mm/h, hemoglobin 9.8 g/dl, leukocyte count 7300/mm^3 with a normal differential, platelet count 182,000/mm^3, urea 41 mg/dl, creatinine 0.9 mg/dl, glucose 91 mg/dl, total protein 7.5 g/dl, and albumin 3.5 g/dl. Serum electrolytes, alanine

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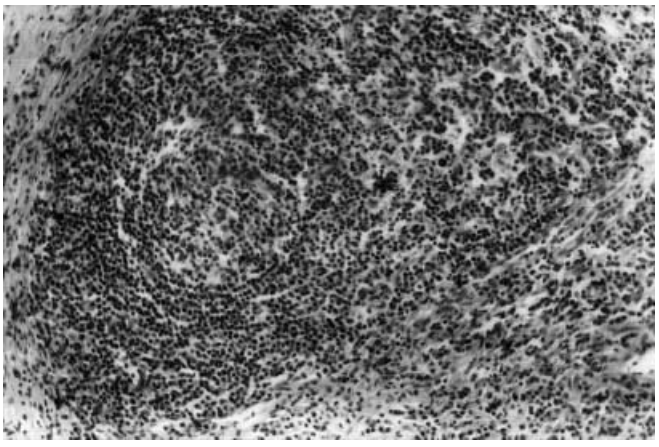

Fig. 1 A lymphoid follicle with regressive transformation of the germinal centers in the lymph node and many plasma cells are seen in the interfollicular area. H&E, ×200

aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyltranspeptidase (GGT), bilirubins, and lactic dehydrogenase (LDH) were normal. Urinalysis was normal and there was no albumin. Creatinine clearance was 79 ml/min. Bence-Jones proteinuria in a 24-h urine sample was negative. The serum haptoglobin level was 496 mg/dl (NR: 50–320), serum ferritin level 620 ng/ml (NR: 20–340), serum iron level 122 µg/dl (NR: 5–150), and serum iron binding capacity 285 µg/dl (NR: 250–400). Protein immunoelectrophoresis revealed polyclonal gammopathy. Urine immunoelectrophoresis was normal. Immunoglobulin quantitations were within normal limits. Serologic tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) were negative. The electrocardiograph and chest radiograph were normal. Abdominopelvic ultrasonography revealed hepatosplenomegaly.

Mammary ultrasonography and mammography were performed: both were normal. The esophagogastric studies revealed no pathologic finding. Upper gastrointestinal endoscopy demonstrated extrinsic compression of the gastric fundus. Biopsies obtained from all parts of the stomach revealed no pathology other than gastritis. An abdominopelvic computed tomography (CT) scan confirmed the presence of aortocaval and retroperitoneal lymphadenopathy together with hepatosplenomegaly. The left axillary lymph node was biopsied and microscopic examination was compatible with nonspecific, reactive hyperplasia. Later, the histopathological examination of the excised left supraclavicular lymph node yielded germinal centers with sheets of plasma cells in the interfollicular areas, which was compatible with CD, plasma cell type (Fig. 1). The bone marrow biopsy was normal. As the patient had multicentric disease, surgery was not considered; rather, it was planned to administer her high-dose corticosteroid therapy. However, the patient objected to this. Her complaints regressed following symptomatic treatment and she was discharged to come to regular follow-up visits.

The patient was admitted to our hospital again 14 months later with the complaint of pretibial edema. Laboratory findings were as follows: ESR 110 mm/h, hemoglobin 10.2 g/dl, urea 45 mg/dl, creatinine 1.2 mg/dl, total protein 5.1 g/dl, albumin 2.6 g/dl, total cholesterol 378 mg/dl, and triglyceride 295 mg/dl. Urinalysis revealed 3+ albumin, and oval fat bodies were identified. Proteinuria was 6 g/24 h; Bence-Jones proteinuria was not present. Rheumatoid factor, antinuclear antibodies, cryoglobulins, antineutrophil cytoplasmic autoantibodies (p-ANCA, c-ANCA), C3, and C4 complement levels were normal. Renal ultrasonography revealed kidneys with increased sizes and echogenities. The same lymphoid mass persisted in the abdominopelvic CT. The histopathological examination of the renal biopsy specimen demonstrated disruption of the glomerular architecture due to amyloid deposition, which stained positive with Congo red and was sensitive to treatment with potassium permanganate, compatible with secondary amyloidosis. Once more, the patient resisted chemotherapy. She was discharged again after symptomatic treatment and did not come to regular follow-up visits. The patient was invited to hospital in March 2001 for a detailed clinical and laboratory work-up. The physical examination was normal with no lymphadenopathy or organomegaly. The whole blood count, urea, creatinine, albumin, and lipids were all normal. Urinalysis revealed no proteinuria. Abdominopelvic CT revealed no lymphadenopathy in the abdomen.

Discussion

CD is thought to occur as a result of chronic antigenic stimulation due to an unknown infectious or inflammatory etiology [10]. It has a heterogeneous course: the symptoms persist in some cases for as long as 15 years [11] and have a progressive fatal course in others [12]. Renal dysfunction in the form of nephrotic syndrome is quite a rare occurrence in CD. Some cases of minimal change disease, membranous glomerulonephritis, membranoproliferative glomerulonephritis, or focal glomerulosclerosis have been reported [13].

Secondary amyloidosis is associated with recurrent infections (e.g., tuberculosis, bronchiectasis), chronic inflammatory diseases (e.g., rheumatoid arthritis), familial Mediterranean fever, and some neoplasms (Hodgkin's disease, renal cell carcinoma) [14]. It was shown that high levels of interleukin-6 (IL-6) was produced in germinal centers of hyperplastic lymph nodes in patients with plasma cell type CD [15]. IL-6 leads to the production of acute phase proteins, including serum amyloid A protein, in the liver, and this in turn may result in secondary amyloidosis [15].

Secondary amyloidosis (AA type) due to CD has also been reported in a few case reports. In a MEDLINE search, we could identify 17 cases of CD with secondary amyloidosis. In this report, we present the 18th case. The main features of patients with amyloidosis secondary to CD are shown in Table 1. The majority of them presented with nephrotic syndrome. Most patients had PC type CD, less frequently mixed type CD; only one patient had HV subtype. Sixteen patients had unicentric disease, mostly localized in the abdomen, and only two (including our case) had multicentric disease. Some authors showed that abdominal, especially mesenteric, cases of CD were more frequently associated with secondary amyloidosis than thoracic cases [16].

The therapy for CD and as expected for amyloidosis secondary to CD is not known with certainty. In the review by Bowne et al. [9], complete surgical resection of unicentric disease was proposed to be the best treatment for CD. They suggested that radiotherapy might be used for patients with surgical risks or unresectable lesions [9].

The ideal form of treatment in multicentric CD is more controversial. Partial resection of the tumor mass might provide transient relief of the symptoms in some

Table 1 A summary of the general features of CD patients with secondary amyloidosis. *M* male, *F* female, *PC* plasma cell type CD, *HV* hyaline vascular type CD, *GC* glucocorticoids, *CYC* cyclophosphamide, *L-PAM* melphalan, *Anti-IL-6 RA* murine anti-interleukin-6 monoclonal antibody, *Colc* colchicine, *HD* hemodialysis, *ESRD* end-stage renal disease, *PE* plasma exchange, *NR* no response

Author	Age/sex	Histology	Treatment	Outcome
Pilon et al. [21]	20/M	PC	GC	Deceased
Bonneau et al. [22]	36/M	PC	Not detailed	Improved
Chan et al. [18]	52/M	PC	GC, L-PAM	Improved
West et al. [23]	55/M	PC	None	Deceased
Montoli et al. [17]	31/F	HV	Resection	HD
Kazes et al.[7]	48/F	PC	Resection	Improved
Paydaş et al. [20]	28/F	?	Resection, Colc	Improved
Tanaka et al. [24]	53/F	?	Resection	ESRD, HD
Moon et al. [25]	?	PC	?	?
Moon et al. [25]	?	PC	?	?
Arınsoy et al. [26]	17/F	Mixed	Resection	NR
Ikeda et al. [8]	21/F	PC	Resection	Improved
Funabiki et al. [13]	49/M	?	PE, GC, CYC	Improved
Nishimoto et al. [19]	59/F	PC	Anti-IL-6 RA	Improved
Nishimoto et al. [19]	23/M	Mixed	Anti-IL-6 RA	Improved
Nishimoto et al. [19]	51/M	PC	GC, L-PAM, Anti-IL-6 RA	Improved
Keven et al. [27]	?	Mixed	Resection	Improved
Our case	51/F	PC	None	Improved

cases; however, it provides no long-term benefit [16]. Low-dose radiotherapy might be used in limited cases [9]. The use of corticosteroids alone or together with chemotherapeutic agents yields conflicting results [9].

The first case of multicentric CD with secondary amyloidosis also had pure red cell aplasia; she was treated effectively with methylprednisone and cyclophosphamide [17]. Melphalan might be used as an adjunct to glucocorticoids with satisfactory results [18, 19]. Colchicine was used after resection of the tumorous mass in one patient; it caused regression of the patient's nephrotic syndrome [20]. Humanized anti-IL-6 receptor antibody was administered to three CD patients with secondary amyloidosis; it improved the extent of lymphadenopathy, symptoms, and biochemical abnormalities. Thus, it might be used in refractory forms of the disease [19]. The most important difference that distinguishes this case from others is that our patient's clinical symptoms, nephrotic syndrome and lymphadenopathy in the abdomen, regressed without any specific therapy.

We present a patient with CD who developed nephrotic syndrome due to secondary amyloidosis. As the patient did not accept any treatment modality, medical therapy could not be used. However, 7 years after the diagnosis of CD and 6 years after the diagnosis of secondary amyloidosis, all disease signs and symptoms were absent. This case also proves that some cases of CD proceed rapidly with a fatal outcome, while others might have a relatively benign course. Still, therapeutic alternatives must be offered to all patients.

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