Castleman's Disease: A Study Of A Rare Lymphoproliferative Disorder In A University Hospital

A. M. Al-Amri, I. S. Abdul-Rahman, K. Q. Ghallab

King Fahd University Hospital. King Faisal University, Saudi Arabia.

Abstract

Castleman's disease (CD) is a group of rare lymphoproliferative disorders sharing characteristic clinical and histological features, and usually accompanied by a marked systemic inflammatory response. Two histological patterns of lymph nodes were described: the hyaline-vascular and plasma-cell types. The former is more common (80-90%) and tends to be localized. The plasma cell type is more aggressive and usually multicentric. It is interesting that the inflammatory manifestations seem to be related to a lymph node lesion, because the systemic symptoms and inflammatory activity can return to normal after surgical excision or successful medical treatment of the disease.

We report here our 15-year experience with this rare disease in King Fahd Hospital of the University, Al-Khobar, Saudi Arabia, focusing on the clinical features, therapy, and patients' outcome.

Key words

Castleman's disease, hyaline vascular, plasma cell, multicentric, polyclonal gammopathy, IL-6.

Introduction

Castleman and Towne1 described a disease presenting as a mediastinal mass resembling thymoma. It is also known as "giant lymph node hyperplasia", "lymph node hamartoma", "angiofollicular mediastinal lymph node hyperplasia", and "angiomatous lymphoid hyperplasia". The pathogenesis is unknown, but the bulk of evidence points toward faulty immune regulation, resulting in excessive B-lymphocyte and plasma-cell proliferation in lymphatic tissue. In addition to the mediastinal presentation, extrathoracic involvement in the neck, axilla, mesentery, pelvis, pancreas, adrenal gland, and retroperitoneum also have been described. There are 2 major pathologic variations of Castleman's disease2: (1) hyaline-vascular type, the most frequent, characterized by small hyaline-vascular follicles and capillary proliferation; and (2) the plasma-cell type, in which large lymphoid follicles are separated by sheets of plasma cells. The hyaline-vascular cases usually are largely asymptomatic, whereas the less common plasma-cell variant may present with fever, anemia, weight loss, and night sweats, along with polyclonal hypergammaglobulinemia. Castleman's disease is a rare lymphoproliferative disorder. Few cases have been described world wide. We are describing 8 cases of Castleman's disease which have been diagnosed over the last 15 years at King Fahd Hospital of the University in Saudi Arabia.

Correspondance: Dr. Ibrahiem Saeed Abdul-Rahman, Internal Medicine Department, King Fahd Hospital Of The University, Al-Khobar, 31952, Saudi Arabia,
P. O. Box: 40032, Email: Isaeed99@yahoo.com

Material & Methods

Patients

This is a retrospective study, in which the records of all patients who had lymph node resection at King Fahd Hospital of the University, for the last 15 years were studied. All cases with pathological findings consistent with CD of the hyaline vascular or the plasma cell variant were included in this study. An independent pathologist examined the histologic features of the lymph nodes and/or other tissues collected from the patients and confirmed the histologic diagnosis. None of the patients had autoimmune diseases such as rheumatoid arthritis or Sjögren syndrome.

Serum protein assays

Serum concentrations of C-reactive protein (CRP) and serum amyloid A protein (if needed) were measured by commercial automated immunoassays with lower detection limits of 0.2 mg/l and 0.7 mg/l respectively.

IL-6 values

Were measured by commercial enzyme immunoassay (Biosource International). Values above 4 pg/ml are considered abnormal.

Statistical analysis

Only simple tests (average, mean, percentages) are used because of the small number of patients due to rarity of cases.

Results

Case histories

Patient 1

A 24-year old female patient was referred to us from a local dispensary because of 6-month history of unilateral neck swellings. She was otherwise healthy. The patient asked for medical advice because of a cosmetic reason. Physical examination was normal apart from enlarged right lower deep cervical lymph nodes. The lymph nodes were discrete, firm, mobile, non-tender, and not attached to the skin or underlying structures. There were no other palpable lymph nodes. Abdominal, chest, cardiac, and neurological examinations were normal. Laboratory investigations were as follows: hemoglobin 11.6 g/dl, white cell count, 6.450/mm3; erythrocyte sedimentation rate (ESR), 96 mm/h; blood urea nitrogen, 12; creatinine 1.0 mg/dl; albumin 3.7 g/dl; serum immunoglobulin: IgG 13.2 g/L; IgA 3.4 g/L; IgM 2.72 g/L; C3 and C4 normal; antinuclear antibody (ANA)-negative; rheumatoid factor-negative; C-reactive protein (CRP), 100 mg/L; serum iron, TIBC, ferritin, B12, and folic acid levels were within normal range. Cryoglobulin was negative. Serologic test results were as follows: hepatitis B antigen and antibody (-), hepatitis C antibody (-), anti-HIV (-).Tuberculin skin test (PPD) was negative with 3 and 5 units intradermally. Protein electrophoresis showed mild polyclonal hyper-globulinemia. Urine analysis was negative. Chest radiograph and thorax tomography were normal as well as abdominal ultrasound. One cervical lymph node was removed. In gross appearance, the surface of the mass was pinkish gray and well encapsulated. The histopathologic examination showed diffuse follicular appearance with the characteristic features of Castleman's disease. Lymphoid follicles contained vascular structures in their germinal centers with hyaline-like changes. There were no plasma cells in the interfollicular areas. The picture was consistent with the hyaline vascular type of Castleman's disease (Figure 1).

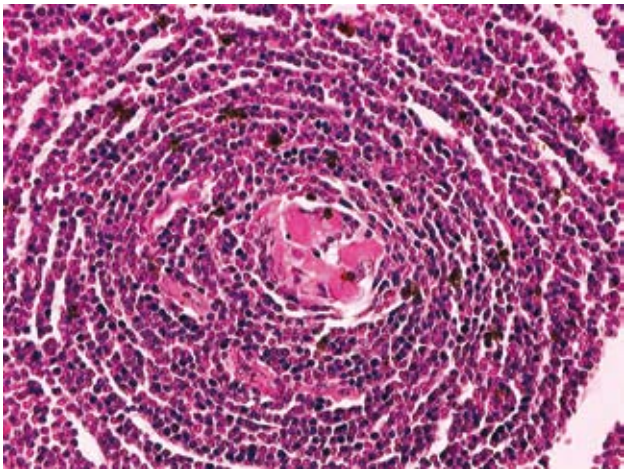

Fig. 1 : CD: hyaline vascular type. Lymphoid follicles stained with H&E, contained vascular structures in their germinal centers with hyaline-like changes. No plasma cells in the inter-follicular areas. Original magnification X 200.

Patient 2

A 52 year-old male patient presented with abdominal discomfort and four-month history of diarrhea. Physical examination showed non-tender central intra-abdominal mass. Complete blood count was as follows: WBC, 8.700; hemoglobin, 10.8 g/dl; platelets, 450,000/cmm. ESR was 70 mm/h. Liver and renal function tests were normal except for serum albumin of 2.2 gm/dl. Tuberculin test was 7 mm after 5 units intradermally. Urine and stool analysis and cultures were negative. Serum IL-6 was 11.8 pg/ml. Abdominal ultrasonography examination and computed CT scan (Figure 2) depicted a heterogeneous solid mass measuring 5.8 X 5.0 cm with no organ enlargement. Chest radiograph and tomography were normal.

At laparoscopy the tumor was found to arise

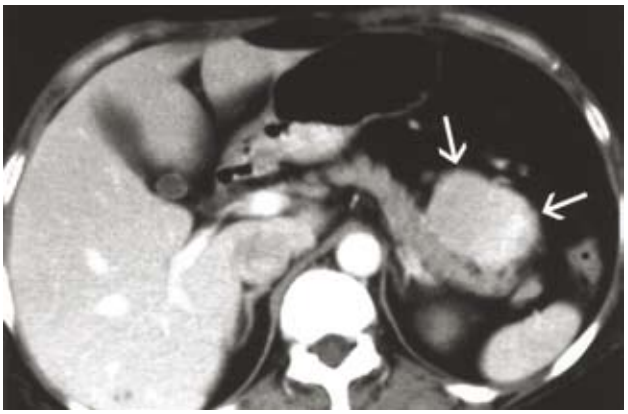

Fig. 2 : CT scan of the abdomen in a patient with CD showing heterogenous solid mass with no organ enlargement. At laparoscopy the tumor was found to arise from the mesenteric lymph nodes.

from the mesenteric lymph node group and was not attached to any organs. It was resected easily. Histologic examination yielded the diagnosis of Castleman's disease; the hyaline-vascular type.

The patient's recovery was uncomplicated, and he remains healthy and free of disease 4 years later.

Patient 3

A 56-year old Indian professor presented with 5-months history of fever spikes, abdominal pain, loss of appetite and weight. During hospital stay he developed progressively increasing jaundice and abdominal distension. Physical examination showed ill looking man who was also pale and jaundiced. A tiny lymph node was palpated in the right supraclavicular group which was unapproachable to surgeons. Chest examination showed right-side pleural effusion, while cardiac examination was normal. Abdominal examination revealed hepatosplenomegaly and ascites. There was +3 pretibial edema, and sensory polyneuropathy. Laboratory investigations were as follows: hemoglobin, 8.4 g/dl, white cell count, 3,100/cmm, and platelets, 66,000/cmm; anemia as normocytic. Serum bilirubin, 5.8; direct bilirubin; 4.0 mg/dl; SGOT, 136; SGPT, 240; GGTP; 545; alkaline phosphatase, 422; LDH, 372 IU/L; albumin, 1.6 and protein 8.0 gm/dl. ESR was 112mm/h; BUN, 78; and creatinine, 1.8 mg/dl. Serum ferritin, folic acid, and B12 levels were normal. Twenty-four hour urine protein was 660 mg, and urinary Bence-Jones protein was negative. Cryoglobulin was negative; rheumatoid factor, and ANA were both positive. Serum protein electrophoresis showed polyclonal hyper-globulinemia. Hepatitis B antigen, hepatitis C antibody, and anti-HIV were negative. Alpha-feto- protein, and carcinoembryonic antigen were normal. Bone marrow biopsy was normal. The ascetic fluid was transudate with negative culture and negative cytology. Abdominal CT scan showed hepatosplenoegaly, and multiple mesenteric lymph nodes. At laparotomy multiple mesenteric and celiac lymph nodes were found; some of them were compressing the common bile duct; biopsies were taken. Histologic examination yielded the diagnosis of Castleman's disease; the plasma cell disseminated type (Figure 3). The patient was treated with systemic steroids and cyclophosphamide, but he died after two weeks from onset of therapy because of disseminated intravascular coagulopathy.

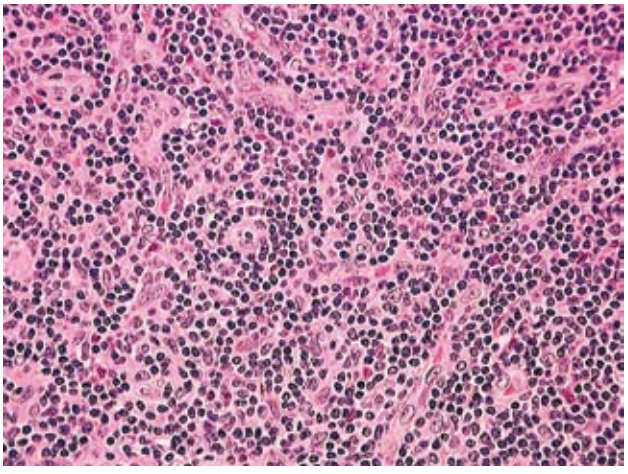

Fig. 3 : CD, plasma cell disseminated type. H&E stain. Original magnification X 100.

Patient 4

A 47-year old male patient was admitted to the hospital because of dyspnea on exertion, dry cough and fever for three months. He was seen in another hospital and treated with different antibiotics and bronchodilators; his symptoms improved. Later on, cough and fever recurred with aggravation of dyspnea and wheezing. In addition he noticed erythematous skin rash all over his upper and lower limbs. Initially the skin rash was interpreted as drug eruptions, treated with antihistaminics without improvement. He was then referred to our hospital. Upon

examination, temperature ranged from 38.0-39.5 °C. Macular skin rash was found on both upper and lower limbs. Right upper deep cervical and bilateral axillary lymph nodes, which were firm, mobile and non-tender. Jugular venous pressure was normal. Chest examination showed diffuse bilateral expiratory bronchi, while cardiac examination was normal. The abdomen was soft and lax with palpable liver and spleen. The remainder of the examination was normal. Laboratory investigations were as follows: Hgb, 10.2 and then dropped to 8.6 gm/dl after 4 days; white cell count 5,600/cmm; neutrophils 62%, lymphocytes 28%, eosinophils 8%, monocytes 2%, platelets 58,000/cmm, reticulocytes 2.7%, erythrocyte sedimentation rate 140 mm/hr, random blood sugar 133 mg/dl, serum sodium 125, potassium 4.3 mEq/L, blood urea nitrogen 22, serum creatinine 1.4 mg/dl; alkaline phosphatase 122, aspartate aminotransferase 90, alanine aminotransferase 68, lactate dehydrogenase 292 U/liter, serum protein 8.2 and albumin 2.3 g/dl; urine analysis showed protein 2+, red cells 2-4, white cells 2-5 per high power field. Specimens for salmonella, brucella, fungal, Ebstein-barr virus, hepatitis, legionella, as well as blood and urine cultures were all negative. Antinuclear antibody titer was 1:1280, homogenous pattern, anti-double strand DNA was negative, and complement levels were normal. Serum IL-6 was110.5 pg/ml. Urine protein in 24 hours was 520 mg. There was hypergammaglobulinemia; a polyclonal pattern. CT scanning of the chest, abdomen and pelvis showed multiple nodular opacities in both hilar areas, multiple enlarged lymph nodes in the left para-aortic region and in the peripancreatic space; in addition both the liver and spleen were enlarged with nodular splenic calcifications. Bone marrow aspirations and biopsies were negative for acid fast bacilli, bacterial cultures, fungi, granulomas or malignancies; it was otherwise hypercellular (Figure 4). Two cervical lymph nodes were totally removed and examined; many of the lymphoid follicles displayed atrophic germinal centers, and mantle zone expanded by large plasma cells (Figure 5). These cells expressed monotypic IgM lambda on both immunohistochemical analysis and in situ hybridization. These features are characteristic of the multicentric Castleman's disease (MCD).

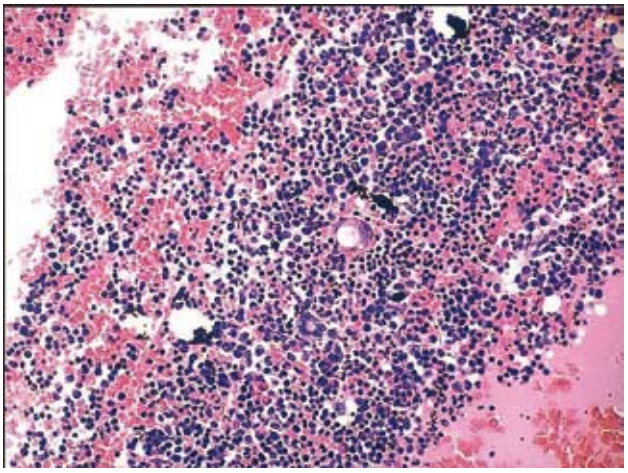

Fig. 4 : Bone marrow biopsy in a patient with CD showing hypercellular bone marrow. H&E stain. Original magnification X 100.

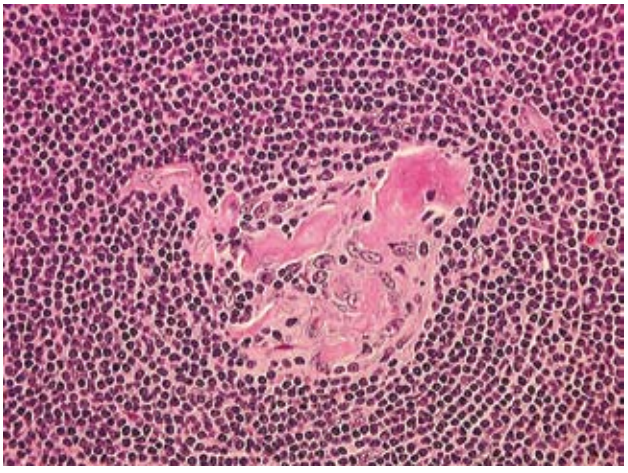

Fig. 5 : Lymph node biopsy in multicentric CD with atrophic germinal center and mantle zone expanded by large plasma cells. H&E stain. Original magnification X 100.

The patient was treated with high dose of intravenous methylprednisolone plus anti-CD20 monoclonal antibody rituximab (Rituxan; Hoffman-La Roche, Basel, Switzerland). The liver size regressed to normal, fever disappeared, and chest condition improved, but splenomegaly persisted. He is still on regular follow-up.

Patient 5

A 34-year male patient with a history of an axillary swelling for at least 2 years, presented to our hospital with postural dizziness, facial and lower limbs edema, in addition to dyspnea on exertion. Upon examination, he looked

pale, with eyelid swellings, but no jaundice or cyanosis. Supine blood pressure was 144/86, and standing 110/64 mmHg. Internal jugular venous pressure was 12 cm H^2O. Multiple lymph nodes were palpable in the left axillary area; they were firm, mobile, smooth, discrete, and non-tender. Other lymph nodes could not be palpated. Chest examination showed bilateral pleural effusion, and cardiac evaluation was normal. Abdominal examination was normal except for ascites. The kidneys were not palpable. Musculoskeletal system including all the joints were free. There was 4+ pitting edema of both lower limbs, the distal pulsations were all intact. Investigations were as follows: CBC: WBC, 6.700/cmm; Hgb, 9.4 gm/dl; platelets, 410000/cmm; ESR, 88 mm/h, ASOT and CRP, non-reactive. ANA, rheumatoid factor, antineutrophil cytoplasmic antibody (ANCA), and anti-DNA were negative; liver function tests were normal except for serum protein, 8.9 gm/dl and serum albumin, 1.1 gm/dl; HCV-antibody, HBs antigen, and HIV antibodies were all negative; urine analysis, protein >300 mg/dl with granular casts, 24-hours urine protein, 11.8 gm; BUN, 44 mg/dl; serum creatinine, 2.1 mg/dl; serum protein electrophoresis, monoclonal gammopathy; serum IL-6, 91.7 pg/ml; chest X ray, normal cardiac shadow with bilateral pleural effusion; ECHO cardiography, normal sized cardiac chambers and valves with normal fractional shortening and no pericardial effusion; serum iron, TIBC, and serum ferritin were normal; abdominal ultrasonography revealed normal size liver and spleen but bulky kidneys on both sides. The pleural and ascetic fluids were transudative with negative bacterial and fungal cultures. All the right axillary lymph nodes were removed and examined; it was interpreted as Castleman's disease, mixed type. Kidney biopsy was performed under local anesthesia; the renal tissue was examined histologically and it showed amyloid deposits (Figure 6). The diagnosis of AA-amyloid type was confirmed. IV methylprednisolone and IV cyclophosphamide were started

Follow-up: two weeks following lymph node excision and the IV medications; lower limb and facial edema subsided. Ascites and pleural effusion disappeared in two month-

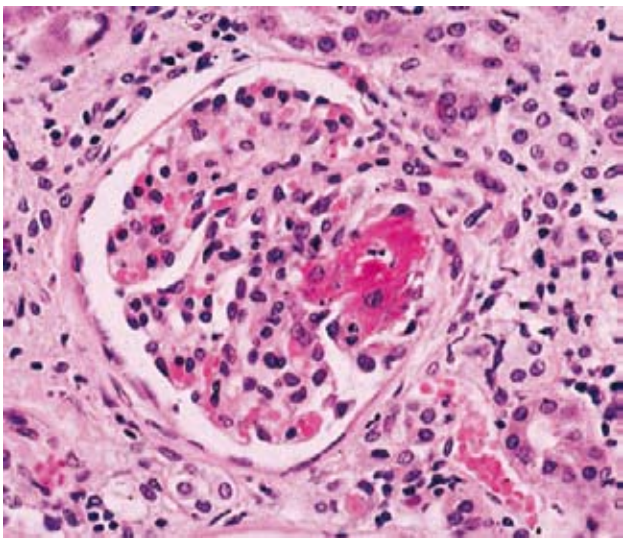

Fig. 6 : Kidney biopsy stained with Congo red in a patient with CD complicated by amyloidosis. Original magnification X 200.

time. Repeated 24 h urinary protein was 3.1 gm. The patient was followed-up on no treatment. Throughout the 7- years follow-up, he has no complaint, renal functions were normal, and 24-h urinary protein <300 mg.

Patient 6

17-year schoolgirl was seen in the outpatient department with 11-months history of left cervical swellings, and a 3-months history of fever, loss of appetite and weight. She had no respiratory, cardiac, gastrointestinal, or central nervous manifestations. There was no history of contact with infected patients, raw milk ingestion or traveling abroad. On examination, she was pale but not jaundiced. Temperature was 39.8 °C, blood pressure 110/70 mmHg & respiratory rate 16/min. Head and neck examination was normal except for bilateral cervical (submandibular, submental, upper and lower deep cervical) lymph nodes; the biggest was 4 X 3 cm, and the smallest was 1 X 0.5 cm. All the lymph nodes were discrete, firm, easily mobile, non tender, with smooth surface and normal skin overlying it. Chest, heart, musculoskeletal, and CNS examination were all normal. The abdomen was lax, freely mobile and non-tender; splenomegaly; no ascites or abdominal bruit. Investigations showed the following: WBC, 11.700/cmm; Hgb, 9.7 gm/dl; platelets, 224000/cmm; lymphocytes, 48%; eosinophils, 10%; ESR 102 mm/hr; renal function tests, normal; liver function tests,

normal except for serum albumin of 2.4 gm/dl; antistreptolysin-O titer, 1:160; ANA, 1:1280; anti-DNAds, negative; rheumatoid factor and other autoantibodies, negative; direct and indirect coomb's tests, negative; tuberculin test with 5 units PPD, negative; throat swab, blood, urine and stool cultures, negative; brucella and salmonella agglutination tests, negative; toxoplasma, CMV and lieshmania antibodies, negative; IL-6, 21.4 pg/ml (normal < 4 pg/ml); chest radiogram, abdominal, chest and pelvic CT scan were all normal. Cervical lymph node biopsies (most of the lymph nodes were removed) and histological examination yielded the diagnosis of Castleman's disease; the hyaline vascular type.

Patient 7

A 44-year old nurse had nearly 18 months history of cervical and axillary swellings, night fever, night sweating, loss of appetite, easy fatigability and skin rash over the upper limbs and chest. She was previously treated with empirical anti-TB medications for more than three months (she refused lymph node biopsy) with no response. Once she was tried on antiviral medications because of positive CMV-antibodies (of the IgG type); fever and lymph node enlargement, however did not improve. Upon examination; temperature was always above 38^{o}C; erythematous skin rash allover the upper limbs chest and back. No mouth, tongue or pharyngeal ulcers, although the tongue was coated with what it seemed to be candida and the pharynx was significantly congested. Right metatarsophalyngeal joint of the big toe had evidence of gouty arthritis. The right cervical and both axillary lymph nodes were enlarged; discrete, non-tender, firm and mobile. Chest, heart and abdominal examinations were all normal as well as both breasts. She was thoroughly investigated for a cause of her problems and all we got was a positive throat and nasal swab cultures for MRSA that was sensitive only to vancomycin; Hgb 10.0 gm/dl; ESR 58 mm/h, IL-6 44.8 pg/ml, ANA 1:160 and albumin level of 3.2 g/dl. The dermatologist believed that the skin rash a drug eruption. Skin biopsy confirmed his suspicion, and it turned out that she was using some herbal medication which was stopped upon our advice; the rash gradually fades out. She had axillary lymph node resection. Histological examination yielded the diagnosis of Castleman's disease; the hyaline vascular type.

Patient 8

A 39-year-old diabetic man, a known case of status post kidney transplantation and long-standing left diabetic foot and diabetic neuropathy, presented with progressive shortness of breath, cough, and expectoration of yellow/green sputum for two weeks prior to admission. He had on and off fever for the last 4 months for which he used to be admitted to hospital with bilateral pulmonary infiltrates. Being heavily immunocompromised; he received broad spectrum antibacterial and antiviral medications, with partial remission. A definite micro-organism, however, could not be identified. He had significant inguinal lymph node enlargement for over 20 months; that was always attributed to the left foot infection. During the last admission we noticed that the inguinal lymph nodes got bigger and that there appeared to be a small right supraclavicular lymph node which was 0.5 X 0.5 cm, firm, mobile, smooth, and non-tender. In addition abdominal examination yielded splenomegaly; about 5 cm below the left costal margin, firm and non-tender, the liver span was 11 cm, and there was no ascites. Both hepatitis C and B screenings were negative, as well as HIV testing. ANA was 1:640, rheumatoid factor was positive, Cryoglobulins and other antibodies were not found. Cultures from different places including those from the foot were negative, as well as virology and mycology studies. WBC count was 3.600/cmm; Hgb 7.0 gm/dl, and ESR 130 mm/h. Serum creatinine 2.4 mg/dl, protein was 8.8, albumin 1.5 gm/dl and IL-6 176.0 pg/ml. Serum protein electrophoresis showed monoclonal gammopathy. Urine protein was 1.1 gm/24h, and Bence Jones proteins were negative. Chest X-ray revealed bilateral pulmonary infiltrates and chest CT scan added bilateral mediastinal shadows that were interpreted by the radiologist as mediastinal lymph nodes. Echo cardiography was normal apart from pericardial effusion. Bronchoscopy and broncho-alveolar lavage were negative for malignancy, AFB,

fungus or pneumocystis carinii. Abdominal and pelvic CT scans were negative. Supraclavicular lymph node biopsy showed findings consistent with Castleman's disease; the plasma cell type. The patient was treated with a high dose of intravenous methylprednisolone plus anti-CD20 monoclonal antibody rituximab (Rituxan; Hoffman-La Roche, Basel, Switzerland). Fever disappeared and the lung infiltrates resolved within a 10-day period.

Evaluation of cases

Table 1 shows the demographic and clinical characteristics of patients. All the patients are Saudi; 3 (37.5%) female and 5 (62.5%) male. The average age is 37 years (range 18-56). The mean duration of disease is 12+8 (range 4-24) months. The sites of lymph nodes are as follows: 62.5% cervical, 25% mesenteric and other intra-abdominal, 25% mediastinal, 25% axillary, and 12.5% inguinal. Anemia (defined as hemoglobin < 12.0 gm/dl) was present in all (100%) patients, 87.5% had hypoalbuminemia (serum albumin < 3.5 g/dl), renal impairment (defined as serum creatinine > 1.2 mg/dl) was present in 50%, polyclonal gammopathy in 65% and monoclonal gammopathy in 12.5%, and AA-amyloidosis in 12.5%. All patients (100%) tested for IL-6 had elevated blood values with a range of 11.8-176.0 pg/ml. As for the histological subtypes; 3 (37.5%) patients had the hyaline vascular, 4 (50%) plasma cell type, and 1 (12.5%) mixed.

Table 2 demonstrates the type of treatment and the patients' outcome. One patient (12.5) died during the study period; the cause of death was DIC (disseminated intravascular coagulopathy), 6 (75%) had complete recovery after lymph node resection. Rituximab and chemotherapy were used in 2 (25%) patients with complete response.

Discussion

Angiofollicular lymph node hyperplasia or Castleman's disease (CD) was first described by Castleman and Towne in 1956. It is an uncommon clinicopathologic entity which traditionally has been divided into hyaline vascular and plasma cell types based on histologic differences [4]. From a clinical staging point of view, Castleman's disease is classified into a localized form, and a more generalized lymphoproliferative disorder with more extensive lymph node involvement and severe systemic manifestations referred to as disseminated/multicenteric subgroup with

Patient	Sex	Age	Duration of disease	LN	Histologic diagnosis	Laboratory data							Manifestation/ complication
						Hgb g/dl	Urine protein	SR mm/h	Creatinine mg/dl	Albumin g/dl	ANA	IL-6 pg/ml	
1	F	24	6	C	HV	11.6	-ve	96	1.0	3.7	-ve	NA	LN
2	M	52	2	Ms	PC	10.8	-ve	70	0.8	2.2	-ve	11.8	LN
3	M	56	5	Ms	PC	8.4	+ve	112	1.8	1.6	+ve	NA	Hepatomegaly splenomegaly DIC
4	M	47	3	C & Md	PC	8.6	+ve	140	1.4	1.4	+ve	110.5	Hepatomegaly splenomegaly pneumonitis skin
5	M	34	24	A	Mixed	9.4	+ve	88	2.1	1.1	-ve	91.7	LN AA-Amyloid
6	F	18	11	C	HV	9.7	-ve	102	1.0	2.4	+ve	21.4	LN splenomegaly
7	F	44	18	C & A	HV	10.0	-ve	58	0.9	3.2	+ve	44.8	LN/skin
8	M	21	7	C, I &Md	PC	7.0	+ve	130	2.4	1.5	+ve	176.0	LN/MCG pneumonitis neuritis

C: cervical; Ms: mesenteric; A: axillary; Md: mediastinal; I: inguinal. HV: hyaline vascular; PC: plasma cell type. LN: lymphadenopathy; NA: not available. Skin: skin rash. MCG: monoclonal gammopathy.

Table 1 : shows the distribution of the patients and controls according to sex, age group and HCV results.

Case No	Treatment	Outcome
1	LN resection	Complete response, 9-year follow-up
2	LN resection	Complete response, 4-year follow-up
3	LN resection, prednisolone, cyclophosphamide	No response, DIC, died
4	Prednisolone, rituximab	Complete response, 2-year follow-up
5	LN resection, prednisolone, cyclophosphamide	Remission of amyloidosis, 7-year follow-up
6	LN resection	Complete response, 4-year follow-up
7	LN resection	Complete response, 3-year follow-up
8	LN resection, prednisolone, rituximab	Complete response, 6-month follow-up

Table 2 : Treatment and outcome of the 8 cases with Castleman's disease

or without peripheral neuropathy [5-9]. This division is not absolute as mild peripheral adenopathy and splenomegaly may even be seen in the localized form. The etiology of the disease is unknown, however, a viral etiology resulting in disordered immunoregulation and dysplastic lymphoproliferative process has been postulated [5-7, 10,11]. The clinical presentations of the two types differ with the localized form having a benign outcome, and the disseminated form following a more dire course associated with organomegaly, polyneuropathy, concurrent endocrine gland disease, proteinuria, infections, and skin changes. Various cytokines and growth factors are implicated in the pathology of the disseminated type. Interleukin 6 (IL-6) and vascular endothelial growth factor (VEGF) are the most important among them. Yoshizaki et al[12] noted elevated serum IL-6 concentrations in patients with Castleman's disease that decreased to normal values after lymph node masses had been resected. IL-6 is a pleiotropic cytokine with a wide range of biological activities. It causes proliferation and differentiation of B cells into antibody producing cells, resulting in hyperplastic follicles and lymph node enlargement. IL-6 also increases VEGF secretion, causing angiogenesis, proliferation of vascular muscle cells, and capillary proliferation with endothelial hyperplasia. IL-6 also is responsible for polarization of T lymphocytes to a type 2 cytokine profile leading to autoimmune phenomena, including autoimmune hemolytic anemia, antinuclear antibody positivity, and increased IgE levels. IL-6 induces synthesis of hepatic acute phase reactants and increases the erythrocyte sedimentation rate and C-reactive protein, IgG, serum fibrinogen, and serum amyloid- A protein levels. Systemic manifestations virtually are always associated with increased IL-6 levels [13, 14]. VEGF is expressed strongly in plasma cells in the interfollicular region of the lymph nodes. It can influence and modify the activity of CD and systemic involvement. Autocrine action of VEGF from plasma cells may be responsible for pleural effusion, ascites, edema and proteinuria [15]. It acts by enhancing vascular permeability and was reported to protect and accelerate renal recovery in antiglomerular endothelial antibody-induced thrombotic microangiopathy in rats. Thus, the role of VEGF, whether protective or causative in systemic injury is not precisely known [16]. In the present study, serum IL-6 and VEGF levels were not studied. Other cytokines such as IL-1ß and IL-1α may also play a role [15]. Recently Kaposi's sarcoma associated herpes virus (KSHV or HHV8) which encodes a functional cytokine (vIL-6) has been found in some patients with Castleman's disease suggesting that aberrant IL-6 activity can result from either endogenous or viral sources [17, 18]. CD, the multicenteric form may be associated with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome [19], a multisystemic syndrome associated with plasma cell dyscrasia. In both CD and POEMS syndrome, various cytokines and growth factors are implicated in the pathogenesis of the disease and may be responsible for abnormalities like hypergammglobulinemia, thrombocytopenia, and infiltration of inflammatory cells into the tissues, in addition to splenomegaly, and lymphadenopathy [20]. One of our patients (patient number 3) had hepatosplenoegaly, polyneuropathy, skin changes and thrombocytopenia; however endocrinopathy and monoclonal protein pattern were not seen.

Ultrasonography, CT scan, and magnetic resonance imaging have proven to be useful in the diagnosis of masses located in the

retroperitoneum. However, the images of CD resemble other masses including lymphoma, tuberculosis, sarcoidosis, and retroperitoneal sarcomas [21]. From radiologic and clinical points of view, disseminated CD may be indistinguishable from lymphoma. Ultimately, biopsy of an enlarged lymph node or mass is mandatory for differential diagnosis [22].

Treatment of localized CD not associated with HHV-8 infection generally is surgical resection, with or without radiotherapy [4,14,23,24], this is almost always curable, resulting in rapid resolution of systemic symptoms and laboratory abnormalities. At present, there is no consensus about the optimal management strategy for patients with the multicenteric form of CD. Successful treatment of such patients has been achieved by using combination chemotherapy with or without prednisone, administered at the time of the initial diagnosis. Many cases, however, are refractory to treatment with corticosteroids or chemotherapy [6]. Treatment with interferon- or with anti-CD20 monoclonal antibody rituximab (Rituxan; Hoffman-La Roche, Basel, Switzerland) has resulted in durable clinical remission of the disease; however, these findings are based on a small number of patients [25,26]. Two of our patients (cases 4 & 8) responded favorably to this drug. Dysregulated overproduction of IL-6 from germinal center B cells is implicated in the pathogenesis of MCD [12]. Previous studies demonstrated that anti-IL-6 receptor antibodies dramatically alleviated the symptoms and biochemical abnormalities, although the disease

Reference	Age (years)	Sex	Site of LN	Histological findings	Outcome
42	49	M	Multicentric	PC	Improvement in anemia and RF with cyclophosphamide and prednisolone
43	46	F	Mesentery	PC	Complete remission after resection
43	23	F	Mesentery	PC	Complete remission after resection
35	37	M	Mesentery	Mixed	Complete remission after resection
33	44	M	Axilla	PC	Complete remission after resection
44	31	F	Mediastinum	HV	Resected, ESRD on dialysis, acute phase response, polyclonal gammopathy resolved
45	21	F	Perihepatic	PC	Complete remission after resection
46	53	F	Retroperitoneal	PC	Resected, fall in acute phase response, but ESRD
37	28	F	Mesenteric	Mixed	Complete remission after resection
34	48	F	Mesenteric	PC	Complete remission after resection
47	29	F	Mediastinum	PC	Died after being treated with cyclophosphamide and prednisolone
48	36	M	Mesentery	PC	Complete remission after resection
29	39	M	Multicentric	HV	Partial response after partial resection + prednisolone
49	39	M	Multicentric	PC	Not described
27	59	F	Multicentric	PC	Improved symptoms, RF, and drop of acute phase response after anti-IL 6 receptor antibody
27	51	M	Multicentric	PC	Improved symptoms, RF, and drop of acute phase response after IL-6 receptor antibody
27	23	M	Multicentric	Mixed	Improved symptoms, RF, and drop of acute phase response after IL-6 receptor antibody

PC: plasma cell; HV: hyaline vascular; RF: renal functions; ESRD: end stage renal disease

Table 3 : Characteristics of the previously reported patients with AA amyloidosis complicating Castleman's disease

usually relapsed on cessation of therapyv [24, 27]. Thus, the blockade of IL-6 signaling is considered an attractive approach to treat MCD. However, the long-term efficacy and safety of the humanized anti-human IL-6 receptor antibody need further evaluation.

Twenty-six cases of systemic amyloidosis associated with CD have been reported previously. Seventeen of these had confirmed reactive systemic (AA) amyloidosis (Table 3) [27-29], two were confirmed as AL type derived from monoclonal immunoglobulins, and in the remaining seven the amyloid was not characterized [30, 31]. One of our patients (case-5) with axillary lymphadenopathy had AA amyloidosis complicating MCD. As currently understood, CD is considered to be a heterogenous 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.[32]. When our patient (case 5) was investigated; hepatitis B, hepatitis C, HIV and other infections were ruled out. The autoantibody pattern and the clinical picture did not point to any primary autoimmune disease. Moreover, the axillary mass, from which CD was subsequently diagnosed, had appeared before many of the organ complications, reinforcing our hypothesis that CD was responsible for triggering the inflammatory response with consequent secondary AA-amyloid deposition which in turn was responsible for the nephrotic syndrome and the orthostatic hypotension. The clinical improvement observed in our patient after the removal of the involved lymph nodes supports this hypothesis. The reversal of both amyloidosis and the nephrotic syndrome, however, are controversial issues, based essentially on case reports, since controlled 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 [33, 34] and led to regression of the nephrotic syndrome and of amyloidosis. However, a recent report, although confirming the regression of the nephrotic syndrome after excision of an abdominal lymph node, assumed no regression of renal amyloid deposits one year after surgery [35]. Some reports documented no regression of the nephrotic syndrome after lymph node excision [36, 37], whereas some showed regression with colchicine therapyc [37]. Treatment of such cases with humanized anti-IL-6 receptor antibodies may lead to improvement of the constitutional and systemic manifestations as well as amyloid regression [27, 38-41].

In Summary

we are reporting on a group of patients with a rare disorder, different presentations, and variable outcome. Patients with localized CD who had complete resection of the tumor were cured. Patients with the systemic form who were treated with chemotherapy and rituximab had complete remission.

Acknowledgement

The authors thank the staff of the Pathology Department at King Fahd Hospital of the University, for their valuable help and support during preparation of this study.

References

1. Castleman B, Towne VW. Case report of Massachusetts General Hospital: weekly clinicopathological exercise; founded by Richard C. Cabot. Case 40011. N Engl J Med 1954; 250:26-30.
2. Magrini U, Lucioni M, Incardona P, Boveri E, Paulli M. Castleman's disease: update. Pathologica 2003; 95:227-9.
3. Castleman R, Iverson L, Menedez V. Localized mediastinal lymph node hyperplasia resembling thymoma. Cancer 1956; 9:822-30.
4. Keller AR, Hochholzer L, Castleman B. Hyaline vascular and plasma cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972; 29:670-83.
5. McCarty MJ, Vukelja SJ, Banks P, et al. Angiofollicular lymph node hyperplasia (Castleman's disease). Cancer Treat Rev 1985; 21:291-310.
6. Peterson BA, Frizzerra G. Multicentric Castleman's disease. Semin Oncol 1993; 20:636-47.
7. Weisenberger DD, Nathwani BN, Winberg CD, et al. Multicentric Angiofollicular lymph node hyperplasia. A clinicopathologic study of 16 cases. Hum Pathol

1985; 16:162-72.

8. Frizzera G, Masserelli G, Banks PM, et al. A systemic lymphoproliferative disorder with morphological features of Castleman's disease-pathological findings in 15 patients. Am J Surg Pathol 1983; 7:211-31.
9. Menke DM, Camorias JK, Banks PM. Angiofollicular lymph node hyperplasia. A comparison of unicentric, multicentric, hyaline vascular and plasma cell types of disease by morphometric and clinical analysis. Modern Pathol 1992; 5:525-30.
10. Shahidi H, Myers J, Kvale P. Castleman's disease. Mayo Clin Proc 1995; 70:969-77.
11. Corbellino M, Poirel L, Aubin J, et al. The role of human herpes virus 8 and Epstein-Barr virus in the pathogenesis of giant lymph node hyperplasia (Castleman's disease). Clin Infect Dis 1996; 6:1120-21.
12. Yoshizaki K, Matsuda T, Nishimoto N, et al. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. Blood 1989; 74:1360-67.
13. McClain KL, Natkunam Y, Swerdlow SH: Atypical cellular disorders. Hematology 2004; 283-96.
14. Lui SL, Chan KW, Li FK, et al. Castleman's disease and mesangial proliferative glomerulonephritis: The role of interleukin-6. Nephron 1998; 78:323-27.
15. Leger-Ravet MB, Pauchmaur M, Devergene D, et al. IL-6gene expression in Castleman's disease. Blood 1991; 78:923-30.
16. Seida A, Wada J, Morita Y, et al. Multicentric Castleman's disease associated with glomerular microangiopathy and MPGN-like lesion: Does vascular endothelial cell-derived growth factor play causative or protective roles in renal injury? Am J Kidney Dis 2004; 43:E3-E9.
17. Parravinci C, Corbellino M, Paulli M, et al. Expression of a virus derived cytokine, KSHV-v IL-6 in HIV and seronegative Castleman's disease. Am J Pathol 1997; 151:1517-22.
18. Aoki Y, Jaffe ES, Chang Y, et al. Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpes virus-encoded interleukin-6. Blood 1999; 93:4034-43.
19. Chan JK, Fletcher CD, Hicklin GA, et al. Glomeruloid hemangioma. A distinctive cutaneous lesion of multicentric Castleman's disease associated with POEMS syndrome. Am J Surg Pathol 1990; 14:1036-46.
20. Menegato MA, Canelles MF, Tonutti E, et al. Remission of nephrotic syndrome after thalidomide therapy in a patient with Castleman's disease. Clin Nephrol 2004; 61:352-56.
21. Ko SF, Hsieh MJ, Ng SH, et al. Imaging spectrum of Castleman's disease. Am J Roentgenol 2004; 182:769-75.
22. Zorraquino J, Loureiro C, Elizondo ME, et al. Retroperitoneal Castleman's disease. Surgery 2007; 141:117-18.
23. Frizzera G, Peterson BA, Bayrd ED, et al. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: clinical findings and clinicopathological correlations in 15 patients. J Clin Oncol 1985; 3:1202-16.
24. Beck JT, Hsu SM, Wijdenes J, et al. Alleviation of systemic manifestations of Castleman's disease by monoclonal anti-interleukin-6 antibody. N Engl J Med. 1994; 330:602-605.
25. Simko R, Nagy K, Lombay B, et al. Multicentric Castleman's disease and systemic lupus erythematosus phenotype in a boy with Klienfelter syndrome: long-term disease stabilization with interferon therapy. J Pediatr Hematol Oncol 2000; 22:180-83.
26. Corbellino M, Bestetti G, Scalamogna C, et al. Long-term remission of Kaposi's sarcoma-associated herpes virus-related multicentric Castleman's disease with anti-CD20 monoclonal antibody therapy. Blood 2001; 98:2473-75.
27. Nishimoto N, Sasai M, Shima Y, et al. Improvement in Castleman's disease by humanized anti-interleukin-6-receptor antibody therapy. Blood 2000; 95:56-61.
28. Pilon VA, Gomez LG, Butler JJ. Systemic amyloidosis associated with a benign mesenteric lymphoid mass. Am J Clin Pathol 1982; 78:112-16.
29. Curioni S, D'Amico M, Quartagno R, et al. Castleman's disease with nephrotic syndrome, amyloidosis and autoimmune manifestations. Nephrol Dial Transplant 2001; 16:1475-8.
30. Chan WC, Hargreaves H, Keller J. Giant lymph node hyperplasia with unusual clinicopathologic features. Cancer 1984; 53:2135-9.
31. Miura A, Sato I, Suzuki C. Fatal diarrhea in a patient with Castleman's disease associated with intestinal amyloidosis. Intern Med 1995; 34:1106-9.
32. Bowne WB, Lewis JJ, Filippa DA, et al. The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. Cancer 1999; 85:706-17.
33. Perfetti V, Bellotti V, Maggi A, et al. Reversal of nephrotic syndrome due to reactive amyloidosis after excision of localized Castleman's disease. Am J Hematol 1994; 46:189-93.
34. Kazes I, Deray G, Jacobs C. Castleman's disease and renal amyloidosis. Ann Intern Med 1995; 71:463-64.
35. Keven K, Nergizoglu G, Ales K, et al. Remission of nephrotic syndrome after removal of Castleman's

disease. Am J Kidney Dis 2000; 35:1207-11.

36. Arinsoy T, Yilmaz M, Ataoglu O, et al. Castleman's disease with renal amyloidosis and nephrotic syndrome. Nephrol Dial Transplant 1997; 12:2713-16.

37. Paydas S, Gonlusen G, Sagliker Y. Regression of nephrotic syndrome with colchicine therapy secondary to amyloidosis with associated Castleman's disease. Nephron 1995; 71:463-64.

38. Hawkins PN, Hall M, Hall R, Penny L, Henderson A, Yacoub M, Mitchell A, Pepys MB. Regression of AL amyloidosis and prolonged survival following cardiac transplantation and chemotherapy. In: Kisilevsky R, Benson MD, Frangione B, Gauldie J, Muckle TJ, Young ID, eds. Amyloid and Amyloidosis 1993. Pearl River NY, Parthenon, 1994:657-9.

39. Hawkins PN, Vigushin DM, Richardson S, Seymour A, Holmgren G, Steen L, Wood P, Hall A, Peters AM, Pepys MB. Natural history and regression of amyloidosis. In: Kisilevsky R, Benson MD, Frangione B, Gauldie J, Muckle TJ, Young ID, eds. Amyloid and Amyloidosis 1993. Pearl River NY, Parthenon, 1994:638-41.

40. Hawkins PN, Rydh A, Danielsson A, Cajander S, Hietala S-O, Riklund Ahlstom K, Pepys MB, Suhr O. SAP scintigraphy in familial amyloid polyneuropathy: regression of visceral amyloid following liver transplantation. In Kyle RA, Gertz MA, eds. Amyloid and Amyloidosis 1998. Pearl River NY, Parthenon, 1999:333-35.

41. Gillmore JD, Booth DR, Rela M, et al. Curative hepatorenal transplantation in systemic amyloidosis caused by the Glu526Val fibrinogen □-chain variant in English family. QJ Med 2000; 93:269-75.

42. Funabiki K, Kaneko S, Terajima M, et al. A case of multicentric Castleman's disease associated with renal amyloidosis and pure red cell aplasia. Am J Nephrol 1998; 18:247-50.

43. Ordi J, Grau JM, Junque A, et al. Secondary (AA) amyloidosis associated with Castleman's disease: report of two cases and review of the literature. Am J Clin Pathol 1993; 100:394-7.

44. Montoli A, Minola E, Stabile F, et al. End-stage renal failure from renal amyloidosis of the AA type associated with giant lymph node hyperplasia (Castleman's disease). Am J Nephrol 1995; 15:142-46.

45. Ikeda S, Chisuwa H, Kawasaki S, et al. Systemic reactive amyloidosis associated with Castleman's disease. Serial changes of the concentration of acute phase serum amyloid A and interleukin-6 in serum. J Clin Pathol 1997; 50:965-67.

46. Tanaka K, Horita M, Shibayama H, et al. Secondary amyloidosis associated with Castleman's disease. Intern Med 1995; 34:122-26.

47. Chan KW, Lo WK, Cheng IK. Nephrotic syndrome associated with angiofollicular lymph node hyperplasia and subsequent amyloidosis. Pathology 1992; 24: 229-30.

48. Bonneau R, Paquin F, Giroux L. Angiofollicular lymph node hyperplasia of the plasma cell type with nephrotic syndrome and systemic amyloidosis: an unusual association. Lab Invest 1982; 46:10-11A.

49. Kanoh T, Shimada H, Uchino H, et al. Amyloid goiter with hypothyroidism. Arch Pathol Lab Med 1989; 113:542-44.