Multicentric, Hyaline Vascular Variant of Castleman's Syndrome

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Abstract Castleman's disease is a nonneoplastic adenopathy, also known as angiofollicular or giant lymphnode hyperplasia. Its multicentric form presents with wide spread lymphadenopathy and systemic symptoms. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) is observed in 11–30 % of the patients with Castleman's disease (Dispenzieri et al., Blood 101:2496–2506, 2003). Tuberculosis and lymphoma are the common diagnosis in patients with clinical features of weight loss, lymphadenopathy, hepatosplenomegaly and lymphocyte predominant ascites. We had a similar presentation in a young male, who was a diabetic, with clinical features suggestive of probable tuberculous infiltration of abdomen and adrenals causing addisonian features, lymphocyte predominant ascites, hepatosplenomegaly and generalized lymphadenopathy. However, a pathological diagnosis of hyaline vascular variant of Castleman's disease was obtained on lymphnode biopsy, which propelled us into doing a skeletal survey and bonemarrow biopsy. A final diagnosis of multicentric Castleman's disease with reactive plasmacytosis was achieved. Patient had osteosclerotic lesion in the right femur with evidence of polyneuropathy, organomegaly, endocrinopathies and skin hyperpigmentation. He has improved on chemotherapy with melphan and dexamethasone. Hyaline vascular variant of Castleman's disease rarely presents with systemic symptoms. Follow up is

essential, as they can manifest with complications like POEMS and lymphoma.

Keywords Castleman's disease · POEMS syndrome · Hyaline vascular variant

Case Report

A 32 year old male presented to us with rapid weight loss, darkening of skin, abdominal distension and blurred vision. He had lost over 12 kg in 2 months (Fig. 1a, b). Diabetes was diagnosed 2 years prior to presentation, for which he took tab. glimepiride, however he stopped it in the previous 2 months due to recurrent giddiness. On examination, he weighed 34 kg and was emaciated with a low blood pressure (90/60 mmHg). There was generalized hyperpigmentation, significant cervical and axillary lymph node enlargement and bilateral papilledema. Hepatosplenomegaly and moderate ascites were present. There was no objective sensory loss in the lower limbs.

Suspecting adrenal insufficiency, morning blood sample for random cortisol estimation was drawn and we proceeded with a detailed evaluation of the patient. Investigations revealed a normal complete blood count and peripheral smear. Patient was HIV negative by ELISA. Blood sugars were in the normoglycemic range. Electrolyte abnormalities in the form of hyponatremia and hyperkalemia was present along with deranged renal function (Table 1). Urine microscopy showed granular casts. Twenty-four hour urine protein excretion was 30 mg/day. With adequate hydration, patients renal functions improved to normal. Ascitic fluid analysis revealed high SAAG ascites with 170 cells/ μ l (N39 % L62 %). As the ascitic fluid was lymphocyte predominant, tuberculosis and

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Fig. 1 **a** Old photo of patient for comparison with that at the time of admission. **b** Photo of the patient at the time of admission showing generalised hyperpigmentation and abdominal distension. **c** Osteosclerotic lesion on the anterior aspect of right femur

lymphoma were two possibilities. Tuberculosis was ruled out because the ascitic fluid ADA was low (13.2 IU) and ascitic fluid AFB PCR was negative. Ultrasonography of the abdomen revealed hepatosplenomegaly with normal liver echo texture, no focal lesions, normal portal vein size, free fluid, multiple paraaortic lymph nodes, and omental thickening. Both the kidneys were normal in size with normal corticomedullary differentiation. Contrast enhanced CT abdomen revealed mesenteric, retroperitoneal lymphadenopathy and ascites, with omental thickening suggestive of tuberculosis or lymphoproliferative disorder. Fine needle aspiration cytology from cervical lymph node was suggestive of low grade NHL. For histopathological examination, a lymph node biopsy was performed.

Excision biopsy of the cervical lymph node was reported as Castleman's disease, hyaline vascular variant (Fig. 2a, b). Bone marrow aspiration and biopsy was suggestive of hypercellular marrow with normoblastic erythropoiesis, normal and active leucopoiesis and megakaryopoiesis with interstitial increase in mature plasma cells (9 %). Immunohistochemistry—CD 138+, kappa, lambda dual positive s/o reactive plasmacytosis (Fig. 3a–d). Serum protein electrophoresis was normal. Serum free light chain assay revealed elevated kappa and lambda free light chain {Free kappa: 49.40 (3.3–19.4), free lambda: 95 (5.71–26.3) free light chain ratio: 0.52}, suggesting reactive plasmacytosis. On

skeletal survey, patient was found to have osteosclerotic lesion in the upper end of right femur (Fig. 1c).

Having ruled out tuberculosis and lymphoma and HIV infection, we reached a diagnosis of plasma cell disorder with multicentric Castleman's disease. Suspecting an associated POEMS syndrome, we did synacthen test for adrenal insufficiency, other hormonal profile and nerve conduction test. Serum cortisol at, 8 am, assayed by radioimmunoassay was 13.85 µg/dl. As the serum cortisol was inappropriately low for the stressed state, patient was then subjected to co-syntropin stimulation test. Sixty minutes post co-syntropin injection (250 µg iv), serum cortisol assayed was 17.71 µg/dl, suggesting adrenal insufficiency. Serum testosterone level was low (23 ng/dl). Serum LH and FSH were normal. He had elevated TSH (28.27 µ IU/ml) with low FT3, FT4 (FT3—0.68 ng/ml, FT4—0.38 pg/ml). Patient's blood sugars were under control without requirement of any anti diabetic medications, HbA1C was 6.5 %. Nerve conduction studies showed predominantly demyelinating type of sensory motor polyneuropathy. Patient had papilledema, however CT brain and MRI brain were normal. CSF pressure was normal with no evidence of meningeal inflammation.

Our patient had multicentric hyaline vascular variant of Castleman's disease with reactive plasmacytosis. He also had osteosclerotic lesion in the right femur with evidence of polyneuropathy, organomegaly, endocrinopathies and skin hyperpigmentation. However, our patient did not have monoclonal gammopathy. We think that immunofixation technique, which is more sensitive than serum protein electrophoresis, would have been beneficial for estimating even small amount of monoclonal protein, which may have been missed by serum protein electrophoresis [1, 2]. This could not be done due to lack of this facility at our institute. He had additional features of edema, osteosclerotic lesion, papilledema and ascites, which are commonly seen with Castleman's disease. Amongst the diagnostic criteria needed for POEMS syndrome, our patient satisfied one major and seven minor criteria. Our patient had POEMS like

Table 1 Results of investigations done for this patient

Test	Result	Normal values
Testosterone	23.04 ng/dl	241–827 ng/dl
LH	6.05 m IU/ml	1.5–9.3 m IU/ml
FSH	3.57 m IU/ml	1.4–18.1 m IU/ml
Blood urea	72 mg/dl	15–40 mg/dl
Serum creatinine	2.2 mg/dl	0.7–1.2 mg/dl
Sodium	134 mEq/l	135–145 mEq/l
Potassium	5.4 mEq/l	3.5–5 mEq/l

Fig. 2 **a** Lymphnode biopsy showing follicular hyperplasia (H and E, $\times 100$). **b** High power of a follicle showing an eccentrically placed blood vessel—so called lolly pop appearance (H and E, $\times 400$)

features except for monoclonal plasma cell proliferation, which is a major diagnostic criterion.

Patient was initially started on steroids (prednisolone 5 mg morning and 2.5 mg evening dose) and eltroxin later. Patient's ascites has resolved and lymphadenopathy regressed on melphalan ($2 \text{ mg/m}^2/\text{day}$) and dexamethasone (40 mg/day) chemotherapy.

Discussion

Castleman's disease is a nonneoplastic adenopathy, also known as angiofollicular or giant lymphnode hyperplasia. It can be classified as (a) unicentric versus multicentric, based on clinical and radiological findings, (b) hyaline vascular versus plasmacytic versus mixed cellularity variety based on histopathology and (c) as HIV negative versus HIV positive based on the HIV status of the patient.

Unicentric form presents with localized lymphnode enlargement. Multicentric form presents with wide spread lymphadenopathy with systemic symptoms. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) is observed in 11–30 % of the patients [1]. Hyaline vascular variant presents as localised mediastinal lymph node enlargement with small hyalinised follicles and marked interfollicular vascular proliferation [3]. Pathogenesis is unknown, but dysplastic follicular dendritic cells has been implicated. Vascular proliferation is due to excess VEGF. Plasma cell variant is characterized by sheets of plasma cells with proliferation of blood vessels [3]. Excess IL6 and abnormal plasma cells are possibly related to the pathogenesis.

Multicentric plasma cell variant has been associated with POEMS syndrome.

POEMS syndrome is also known as Crow-Fukase or Takatsuki disease. Two major and one minor criteria are needed for a diagnosis of POEMS syndrome [1, 2]. Major criteria includes polyneuropathy and monoclonal plasma cell proliferative disorder. Minor criteria include the following:

1. Sclerotic bone lesions
2. Castleman disease
3. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
4. Edema (edema, pleural effusion, or ascites)
5. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)
6. Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomas, white nails)
7. Papilledema

Monoclonal plasma cell disorder (bone marrow plasma cell usually $<5\%$ with predominantly lambda restricted monoclonal light chains) and peripheral neuropathy, by definition, are found in all patients with POEMS syndrome. However, in an earlier study of 102 cases of Crow Fukase syndrome, Nakanishi et al. reported that 11 patients had polyclonal proteins. Osteosclerotic lesion was found in 97 % patients in Mayo Clinic study (a series of 99 patients of POEMS syndrome) [1, 2]. Skin changes ranging from thickening, long hair on extremities, hyperhidrosis, clubbing, white nails and angiomatosis is seen in 50–90 % of cases. Hepatosplenomegaly and lymphadenopathy are found frequently in POEMS syndrome. Lymphadenopathy

Fig. 3 **a** Bone marrow aspirate showing increased plasma cells (Giemsa, $\times 100$). **b** Bone marrow biopsy showing increased plasma cells with Russell bodies (H and E, $\times 400$). The plasma cells were immunoreactive for kappa light chains (**c**) as well as lambda light chains (**d**) (IHC, $\times 400$)

is due to Castleman's disease, which is also known as angiofollicular lymphnode hyperplasia, giant benign lymphoma, giant lymphnode hyperplasia or lymphoid hamartoma. Eleven to thirty percent of patients with POEMS syndrome have Castleman's disease [1].

Exact etiology is unknown. Antibodies to HHV8 have been found in 78 % of patients with POEMS syndrome [2, 4]. Overproduction of cytokines like vascular endothelial growth factor, interleukin 6 and TNF- α has been postulated to cause increased vascular permeability leading to edema, ascites and papilledema and organomegaly [5, 6]. Peripheral neuropathy may be due to microthrombi in the endoneurial blood vessel.

Very few cases of multicentric hyaline vascular variant of Castleman's disease with POEMS have been reported worldwide. Hyaline vascular variant are usually localized in the form of mediastinal adenopathy. Our patient had hyaline vascular variant of Castleman's disease with multicentric presentation. He also had osteosclerotic lesion in the right femur with evidence of polyneuropathy, organomegaly, endocrinopathies and skin hyperpigmentation. Though he did not satisfy one of the major diagnostic criteria for POEMS, he had several manifestations of this syndrome. This case is being reported because of the rarity of hyaline vascular variant of Castleman's disease presenting in this fashion and to highlight the diagnostic approach.

References

1. Dispenzieri et al (2003) POEMS syndrome: definitions and long-term outcome. *Blood* 101:2496–2506
2. Dispenzieri A (2005) POEMS syndrome. *Hematology Am Soc Hematol Educ Program* 2005:360–367
3. Cronin DM, Warnke RA (2009) Castleman disease: an update on classification and the spectrum of associated lesions. *Adv Anat Pathol* 16(4):236–246
4. Bélec L, Authier FJ, Mohamed AS, Soubrier M, Gherardi R (1999) Antibodies to human herpesvirus 8 in POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome with multicentric Castleman's disease. *Clin Infect Dis* 28(3):678–679
5. Watanabe O, Maruyama I, Arimura K et al (1998) Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow–Fukase (POEMS) syndrome. *Muscle Nerve* 21:1390–1397
6. Gherardi RK, Bélec L, Fromont G, Divine M, Malapert D, Gaulard P, Degos JD (1994) Elevated levels of interleukin-1 β and IL-6 in serum and increased production of IL-1P mRNA in lymph nodes of patients with polyneuropathy, organomegaly, endocrinopathy, m protein, and skin changes (POEMS) syndrome. *Blood* 83(9): 2587–2593