Castleman disease with features of POEMS syndrome

H M D R Gunathilake[1], N P Madarasingha[2], G M P Sirimanna[3]

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Abstract

Castleman disease is a clincopathological entity, represented by lymphadenopathy, and histologically angiofollicular lymph node hyperplasia. It may be localized or multicentric. Symptoms and signs are mild in localized disease, and remit when the lymph node mass is excised. Mutlicentric Castleman disease, on the other hand, is associated with widespread lymphadenopathy and systemic involvement. It overlaps with POEMS syndrome and carries a poor prognosis. We describe 2 patients with multicentric Castleman disease who had features of POEMS syndrome, including characteristic dermatological manifestations.

Introduction

Castleman disease, also known as angiofollicular lymph node hyperplasia, is a lymphoproliferative disorder, first described by Dr. Benjamin Castleman in 1956[1]. The disorder can be localized (unicentric) or multicentric. In localized disease symptoms and signs are mild and remits completely after surgical removal of involved lymph nodes. Multicentric Castleman disease, on the other hand, is associated with widespread lymphadenopathy and "B" symptoms such as fatigue, fever, night sweats, anorexia and weight loss. It overlaps with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal paraproteinaemia and skin lesions), and has a poor prognosis[2]. Histologically, two variants, namely hyaline and plasma cell types, are described. Less commonly a combination of both types may occur[1]. We report 2 cases of multicentric Castleman disease associated with some features of POEMS syndrome, including characteristic dermatological manifestations.

Case 1

A 45-year-old electrician from Ampara presented with peripheral sensory loss and unsteady gait for 1½ years. He has had asymptomatic brown coloured nodules on the trunk for nearly 20 years (Figure 1). During past 2 years he had developed generalized hyperpigmentation, acquired icthyosis, and hypertrichosis.

He complained of poor appetite and significant weight loss over the past one year. There was no history of fever or night sweats. He had loss of libido and impotence. He had poor exercise tolerance, but no history of angina, orthopnoea, paroxysmal dyspnoea or ankle oedema. He had been investigated for hepatosplenomegaly at the local hospital in April 2004. He was a non-smoker and had never indulged in alcohol.

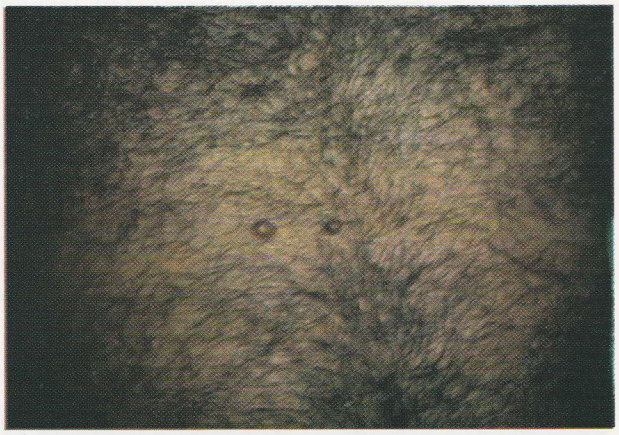

Figure 1. *Hypertrichosis and asymptomatic skin nodules on the trunk.*

On examination he was averagely built, not pale, and had bilateral inguinal lymphadenopathy, generalized hyperpigmentation, icthyosis, hypertrichosis and firm, skin-coloured, non-tender 0.5cm sized nodules on the trunk. He did not have finger clubbing or ankle oedema.

The neurological examination revealed impaired pain, light touch, joint position and vibration sensation over the extremities. The cranial nerves, optic fundi and motor system were normal. He had no cerebellar signs. Romberg's test was positive and the gait was ataxic.

He had 10 cm, firm, non-tender liver with smooth surface and regular margin. 8 cm, firm splenomegaly was present. The cardiovascular and respiratory systems were clinically normal.

The ESR was 14mm 1st hour. The blood count was normal (haemoglobin 13.6 g/dl, WBC 7300/mm^3 N–65%, L–32%, M–2%, E–1.5%, platelets 307,000 mm^3). The blood picture showed reactive lymphocytosis.

[1]*Senior Registrar,* [2]*Registrar,* [3]*Consultant Dermatologist, National Hospital of Sri Lanka, Colombo.*

Renal and liver functions were normal. Nerve conduction studies were compatible with a sensory neuropathy.

Serum proteins were 77 g/l, albumin 42 g/l, and globulin 35 g/l. Serum protein electrophoresis and immunoprecipitation revealed polyclonal elevation of gamma globulins. No monoclonal bands were present. The skeletal survey was normal. Contrast enhanced CT scan of abdomen showed hepatosplenomegaly. The chest radiograph was normal.

Bone marrow examination showed an active marrow with several foci of plasma cells, displaying a normal morphology.

Fasting blood sugar, oral glucose tolerance test, thyroid function tests, and LH and FSH were within normal limits.

Ingiunal lymph node biopsy was consistent with plasma cell type Castleman disease. The histology of skin nodules showed glomeruloid haemanigioma (Figure 2). Liver biopsy showed normal architecture with focal macrovesicular steatosis. Rectal biopsy showed no evidence of amyloidosis. ECG and echocardigraphic assessments were normal. HIV screening was negative.

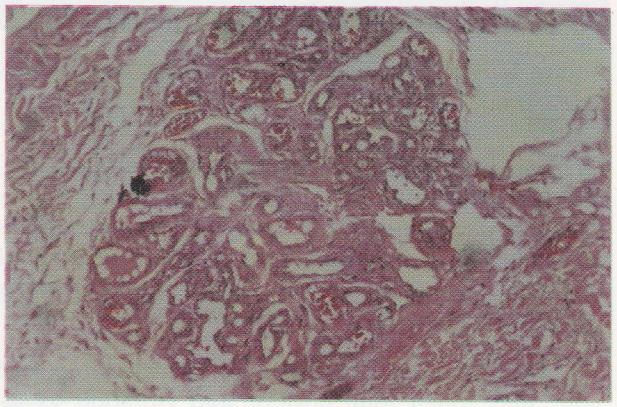

Figure 2. *Glomeruloid haemangioma.*

Case 2

A 44-year-old housewife presented with progressive numbness and weakness of lower limbs for 1 year, and upper limbs for 4 months. She complained of hyperhidrosis and hair loss. She had dypnoea on moderate exertion. She had been previously investigated for erythrocytosis. She had irregular menstrual periods for 1 year and amenorrhoea for past 2 months.

On examination she was averagely built. Mucous membranes were pink. Facial flushing and generalized hyperpigmentation were noted. Right axillary lymph nodes were enlarged. There were 0.5cm sized, skin coloured tumours on the trunk and the proximal upper limbs. She had bilateral ankle oedema.

The cardiovascular and respiratory systems were clinically normal except for the loud second heart sound. Liver was enlarged 10 cm below costal margin. Spleen was just palpable.

The cranial nerves and optic fundi were normal. Mild weakness was noted in lower limbs. Reflexes were globally diminished. Pain and light touch sensations over the extremities were impaired. Joint position sensation was intact. No cerebellar signs were present. Gait was unsteady.

ESR was 8 mm 1st hour. Blood count showed mild erythrocytosis (Haemoglobin 17.4 g/dl, PCV 48%, WBC 9800 mm^3, N–50% L–42% E–4%, platelets 188,000 mm^3). Blood picture was normal. Renal and liver function tests were normal. Nerve conduction tests were consistent with demyelinating sensory motor neuropathy.

Serum proteins were normal (7.1 g/dl, albumin 3.6 g/dl, globulin 3.5 g/dl). Serum protein electrophoresis showed polyclonal increase in gamma-globulins. No monoclonal bands were present.

Bone marrow examination showed increased erythropoiesis with noromoblastic maturation and clusters of plasma cells (15%). Axillary lymph node biopsy was compatible with plasma type Castleman disease. Biopsy of skin nodules showed vascular proliferations.

ECG and Chest radiograph were normal. Echocardiographic findings were suggestive of moderately severe pulmonary hypertension. Arterial blood gas analysis, lung function tests and high resolution CT scan of thorax were normal. Endocrine profile was normal. HIV screening was negative.

Discussion

Castleman disease constitutes a clincopathological entity, represented by adenopathy and histologically angiofollicular lymph node hyperplasia. Usually Castleman disease entails a polyclonal lymphocytic proliferation, though in some cases this can be monoclonal[2].

There are 2 histological types. In the hyaline vascular Castleman disease, lymph nodes show abnormal follicles having poorly formed germinal centers with a central hyalinised blood vessel, surrounded by an expanded mantle zone consisting of concentric rims of small lymphocytes giving an onion skin appearance[4]. In the plasma cell type the germinal centres may have normal looking germinal centres but there is massive interfollicular plasma cell infiltration. The hyaline vascular type is more common

and tends to be localized, while the plasma cell variant tends to be multicentric.

The aetiology of Castleman disease is poorly understood. The hypothesis of a viral infection has been raised. Some studies have suggested a role for human herpes virus 8 (HHV-8), already implicated in Kaposi Sarcoma and primary effusion lymphoma[4]. In multicentric forms HHV-8 sequences have been detected in 60 – 100% of patients infected with HIV and 20 – 40% of those who are not[2]. High circulating levels of interleukin-6 (IL 6) have been observed in these patients. HHV-8 is able to produce an IL 6 homologue (vIL 6) in association with dysregulation of cytokines[5].

Multicentric Castleman disease is nearly always symptomatic. Elevated IL 6 largely accounts for the symptoms. Asthenia (65%), weight loss (67%), fever (69%), polyadenopathy (84%), and organomaegaly (74%) are common. Features of POEMS syndrome are observed in 24% patients with Castleman disease[2].

POEMS syndrome is represented by polyneuropathy, organomegaly, endocrinopathy, M-band paraproteinaemia and skin changes. Approximately 15% of patients with POEMS syndrome have concomitant evidence of Castleman disease (plasma cell variant)[6].

Both these patients had polyneuropathy, organomegaly and some evidence of endocrinopathy (impotence and amenorrhoea). In both patients no monoclonal bands were detectable. M component is present in the serum in 75 – 85% cases of POEMS syndrome. Conventional serum protein electrophoresis may be normal or appear polyclonal in about one third of them. The M proteins could be demonstrated in these patients using immunofixation[6].

Skin changes associated with POEMS syndrome include hyperpigmentation, sclerodermoid changes, hypertrichosis, angiomas, hyperhidrosis, alopecia, clubbing of the fingers, whitening of the proximal nail (Terry nails), Raynaud's phenomenon, flushing, acquired icthyosis, Sweet-like lesions, and vasculitis[6].

Our first patient had generalized hyperpigmentation, acquired icthyosis, and hypertrichosis. Female patient had increased pigmentation, flushing, hyperhidrosis and hair loss. Both of them had angiomas.

Most angiomas seen in persons with POEMS syndrome are histologically consistent with cherry angiomas. The angiomas in a small proportion of patients have the appearance of glomeruli (glomeruloid hemangiomas). This finding may be strongly suggestive of POEMS syndrome, but it is not pathognomonic[7]. Skin biopsy from the first patient showed classical glomeruloid hemangioma.

Other recognized associations of POEMS syndrome include polycythemia, thrombocytosis, restrictive lung disease, pulmonary hypertension, systolic cardiac dysfunction, thrombotic diathesis and renal failure[5]. Our second patient had history of erythrocytosis, and clinical and echocardiographic evidence of pulmonary hypertension.

The best treatment for localized form of Castleman disease is complete surgical excision, which results cure in almost all patients[1, 2]. No consensus exists regarding treatment of the multicenrtic form. Treatment options include surgery, corticosteroids, chemotherapy, interferon alpha[1], antivirals[8] (aciclovir or ganciclovir), all trans retinoic acid[9], thalidomide, anti-IL 6 therapies such as suramin (originally used for tryponasomiasis), and anti-IL 6 antibodies[10].

Despite diversity of available therapies, overall prognosis of multicentric Castleman disease remains poor. The outlook is better when HIV status is negative. Eventually some patients develop non-Hodgkin lymphoma or Kaposi sarcoma.

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