Case Report
Successful combination of melphalan and steroids in Castelman disease variant of POEMS syndrome

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Abstract: Background: Castleman Disease (CD) is a poorly understood lymphoproliferative disease which can be associated with HIV, lymphoma, POEMS syndrome, paraneoplastic pemphigus, and plasma cell dyscrasias. We report a case of CD variant of POEMS syndrome treated with combination of melphalan and steroids. Case report: A 45 year old man presented with gynecomasty, polyseritis, lymphadenectasis and peripheral neuropathy. Laboratory tests found a monoclonal gammopathy, hyperprolactinemia, low testosterone and hypothyroidism. Chest X-rays showed multiple lymphadenectasis, hepatosplenomegaly and polyseritis. Electromyography showed severe axonal polyneuropathy. The cervical lymphadenectasis biopsy reported hyaline vascular CD, multicentric variety. He was treated with cycles of melphalan and prednisone with a favourable evolution. Conclusion: The case meets criteria for multicentric hyaline vascular CD, POEMS variant, treated successfully with melphalan and steroids.

Keywords: Castleman disease, lymphoid hyperplasia, POEMS syndrome

Introduction
Castleman disease (CD), known as angiofollicular lymph node hyperplasia or giant lymph node hyperplasia, was first described by Dr Benjamin Castleman in 1956 who reported 13 cases of unicentric hyaline vascular CD of the chest [1]. CD is a form of nonclonal lymph node hyperplasia and one of the more common causes of nonneoplastic lymphadenopathy [2, 3]. The disease is classified into three types: hyaline vascular disease, plasma cell disease, and mixed type and about 11%-30% of patients are diagnosed with concomitant POEMS syndrome (PS) [4]. This disease offers a wide spectrum of clinical manifestations which makes the diagnosis a challenge [5]. In this report, we describe a patient diagnosed with PS co-existed with CD which is rarely seen.

Case report
A 45 year old man presented with gradual increase in abdominal volume, weakness in limbs and fatigue since a month. He had no history of smoking, alcohol consumption, nor drug abuse. A physical exam revealed white nails (Figure 1. Photo of the fingers showing white nails), localized cutaneous hyperpigmentation of 3 cm of diameter in the anterior surface of the left ankle (Figure 2. Photo of the feet showing localized cutaneous hyperpigmentation of 3 cm of diameter in the anterior surface of the left ankle), weakness in limbs, bilateral gynecomasty, hypoesthesia and hyporeflexia. Abdominal examination showed hepatosplenomegaly and abundant ascitis. He had non-tender enlarged lymph node measuring about 2 cm, spreading in his middle neck triangles.

Laboratory tests found white blood cells 4.5×10^9/L, hemoglobin 12.4 g/L with VGM 87 fl, platelets 316×10^9/L, ferritinemia = 209 ng/ml, creatinine 156 μmol/L, alanine transaminase 6 U/L, aspartate aminotransferase 9 U/L, bilirubin 7.6 μmol/l, gamma GT 20 U/L, PAL 145 U/L, sodium 138 mmol/l, potassium 4 mmol/l, CRP = 8 mg/l, LDH = 245 U/L, CPK = 30 U/L. The serum protein electrophoresis showed albumin 26 g/l, alpha 25.4 g/l, gamma 7.4 g/l with IgG
mmol/l, prolactin 1600 mU/l, FSH = 3.5 mU/ml, LH = 2.4 mU/ml and cortisol 253 mmol/l. All serum tumor markers were within normal range and quantiféron dosage was negative. The β2 microglobulin was elevated 10 times the normal value and IgG4 rate was 2 times the normal value. The Quantiféron* test and all viral serologies (HIV, HHV8, HCV, HBV) were negative. Ascitic fluid cytology was 100% lymphocytic without malignancy and tuberculosis culture was negative. The EMG showed a sensorial severe axonal polyneuropathy of the lower limbs. Computed tomography (CT) scan of the thorax and abdomen revealed polyserositis and multiple lymphadenectasis, a pancreatic enlargement without evidence of malignant tumor. (Figure 3. CT scan of the thorax showed pericardial effusion. Figure 4. CT scan of the abdomen showed abundant ascitis. Figure 5. CT scan of the abdomen showed hepatosplenomegaly. Figure 6. CT scan of the thorax showed polyanneuritis and multiple lymphadenectasis, a pancreatic enlargement without evidence of malignant tumor. Figure 7. CT scan of the thorax showed polyanneuritis and multiple lymphadenectasis, a pancreatic enlargement without evidence of malignant tumor. Figure 8. CT scan of the abdomen showed hepatosplenomegaly, Figure 9. CT scan of the thorax showed pericardial effusion, Figure 10. CT scan of the abdomen showed abundant ascitis, Figure 11. CT scan of the thorax showed polyanneuritis and multiple lymphadenectasis, a pancreatic enlargement without evidence of malignant tumor.)

lambda monoclonal gammopathy at the immuno-electrophoresis. Hormonal tests revealed thyroid stimulating hormone (TSH) 10.776 µU/ml, Free T4 0.62 ng/dl, testosterone 0.83
scan of the abdomen showed coelio mesenteric lymphadenectasis). The pancreatic MRI was normal. Histological examination of the mandibular lymph node showed increased numbers of lymphoid follicles with small, regressed germinal centers and broad mantle zones. The interfollicular areas showed sheets of mature plasma cells (Figure 8A and 8B. Histological examinations stained with hematoxylin and eosin revealed lymphoid hyperplasia and plasma cell infiltration, with interfollicular vascularization, Figure 9. The interfollicular areas showed sheets of mature plasma cells). The immunomarquage of HHV8 was negative. Bone biopsy was normal. The patient was finally diagnosed with CD variant of POEMS syndrome and treated with mensuel cycles of melphalan (0.25 mg/day) and prednisone (2 mg/kg/day) for 4 days/month. The general condition improved, lymphadenomegaly, skin lesions, pericar-

Discussion

CD is a non-clonal lymphoproliferative disease divides into two clinical (unicentric, multicentric) and for histomorphological (hyaline vascular, plasma cell, mixed, plasmablastic) forms [5]. The diversity of its presentation create a pleomorphic picture of this rare entity. The pathogenesis of the syndrome is not well understood. To date, we found that VEGF is the most important cytokine that correlates best with disease activity [6]. The gold standard for diagnosis is an excisional biopsy from the lymph node which retained the diagnosis of multicentric CD in our patient [7]. This entity is thought to comprise several disease entities such as PS [8, 9]. Despite the rarity of ascitis in PS, the diagnosis was made easily since he fulfilled two major criteria and six minor ones. In fact, the diagnosis is based on three of the major criteria.
Castelman disease variant of POEMS syndrome: a rare case

for PS which are polyradiculoneuropathy, clonal plasma cell disorder, sclerotic bone lesions, elevated vascular endothelial growth factor, and CD with at least one of minor features including organomegaly, endocrinopathy, characteristic skin changes, papilledema, extravascular volume overload, and thrombocytosis [10]. Among all these features, neuropathy represent the most frequent described in literature [11]. Despite this frequency, we know that CD has shown a greater clinical spectrum which ranges from fatigue to pleural effusions and organomegaly that may mimic systemic infections or hematologic neoplasms [12]. The treatment with melphalan and steroids was effective and well-tolerated in our patient which is recomended for old patients or those with organ dysfunction in literature [4]. However, autologous peripheral blood stem cell transplantation has become the first-line treatment for younger patients with normal organfunction [13]. In fact, the first reported prospective clinical trial, 3831 patients were treated with 12 cycles of low-dose oral melphalan and dexamethasone and found that 81% of patients had hematologic response, and 100% with at least some neurologic improvement [14]. Also the largest documented cohort in the Czech Republic prefer immunomodulatory drugs for managing CD than rituximab [15]. Only few patients were treated by high dose intravenous immunoglobulin, lenalidomide [16] or monoclonal antibodies, such as rituximab and tocilizumab, without enough evidence of efficacy [17, 18].

Conclusion

CD coexisting with PS is a rare condition of unknown etiology that affects lymphoid tissues in multiple organs and multiple systems making the diagnoses often delayed. The wide spectrum of clinical manifestations makes the diagnosis a challenge. This is one of the reasons that the incidence and prevalence of the disease has not even been well-established. Therefore, it is important that physicians consider this clinical entity so patients can receive adequate and early treatment. The gold standard treatment is melphalan and steroids which improved our patient’s features.

Disclosure of conflict of interest

None.

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References


Figure 9. The interfollicular areas showed sheets of mature plasma cells.
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