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Case Report

Successful combination of melphalan and steroïds 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 steroïds. 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 lympadenectasis, hepatosplenomegaly and polyseritis. Electromyography showed severe axonal polyneuropathy. The cervical lymphadenectasis biopsyreported hyaline vascular CD, multicentric variety. He wastreated with cycles of melphalan and prednisone with a favourable evolution. Conclusion: The case meets criteria for multicentric hyaline vascular CD, POEMS variant, treated successly with melphalan and steroids.

Keywords: Castelman disease, lymphoïd hyperplasia, POEMS syndrome

Introduction

Castleman disease (CD), known as angiofollicular lymphnode 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 amonth. 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 hepatomegaly and abondant ascitis. He had non-tender enlarged lymph node measuring about 2 cm, spreading in his middle neck triangles.

Laboratory tests found white blood cells 4.510× 109/L, hemoglobin 12.4 g/L with VGM 87 fl, platelets 316×109/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

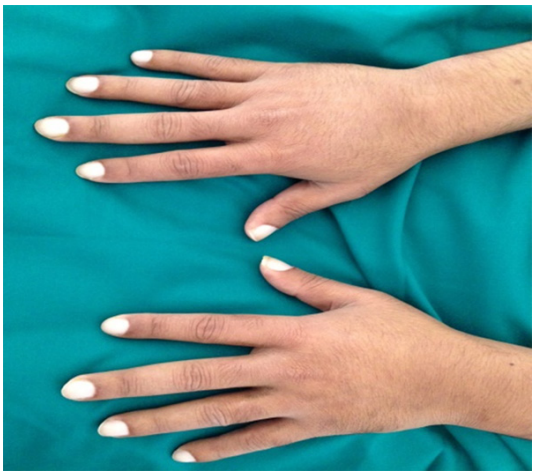

Figure 1. Photo of the fingers showing white nails.

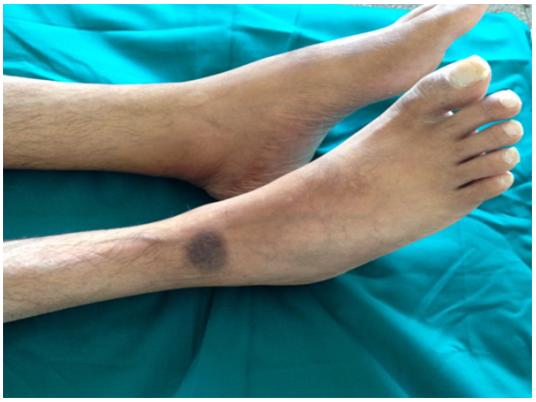

Figure 2. Photo of the feet showing localized cutaneous hyperpigmentation of 3 cm of diameter in the anterior surface of the left ankle.

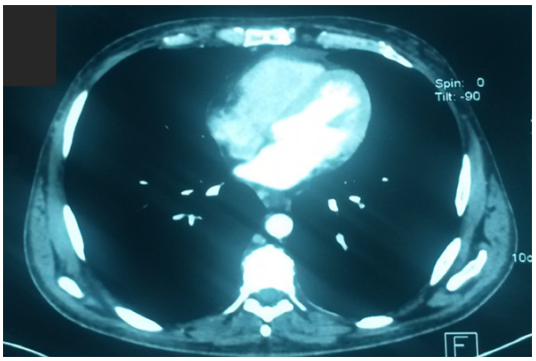

Figure 3. CT scan of the thorax showed pericardial effusion.

lambda monoclonal gammopathy at the immunoelectrophoresis. Hormonal tests revealed thyroid stimulating hormone (TSH) 10.776 µU/ml, Free T4 0.62 ng/dl, testosterone 0.83 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 β^2 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 abondant ascitis, **Figure 5**. CT scan of the abdomen showed hepatoslenomegaly, **Figure 6**. CT scan of the thorax showed pancreatic enlargement, **Figure 7**. CT

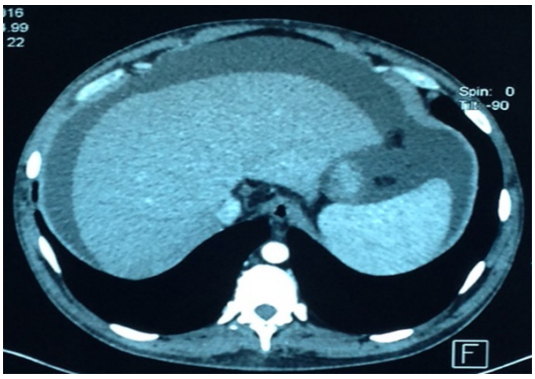

Figure 4. CT scan of the abdomen showed abondant ascitis.

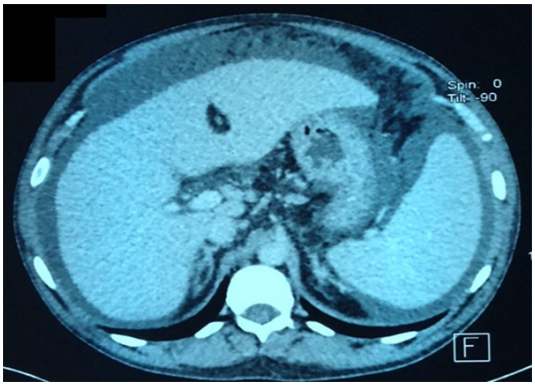

Figure 5. CT scan of the abdomen showed hepatoslenomegaly.

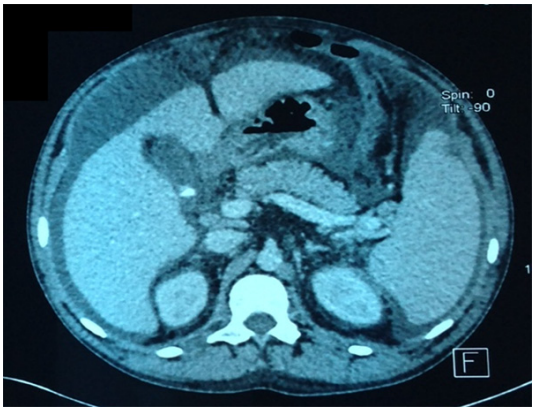

Figure 6. CT scan of the thorax showed pancreatic enlargement.

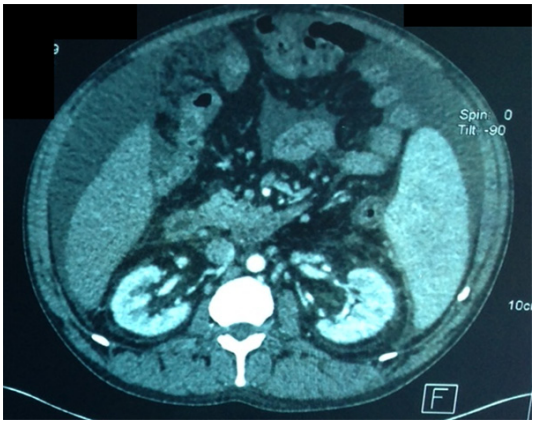

Figure 7. CT scan of the abdomen showed coelio mesenteric lymphadenectasis.

scan of the abdomen showed coelio mesenteric lymphadenectasis). The pancreatic MRI was normal. Histological examination of the mandibulary 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 biopsywas 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, pericardial effusion and ascitis regressed and renal function was restored.

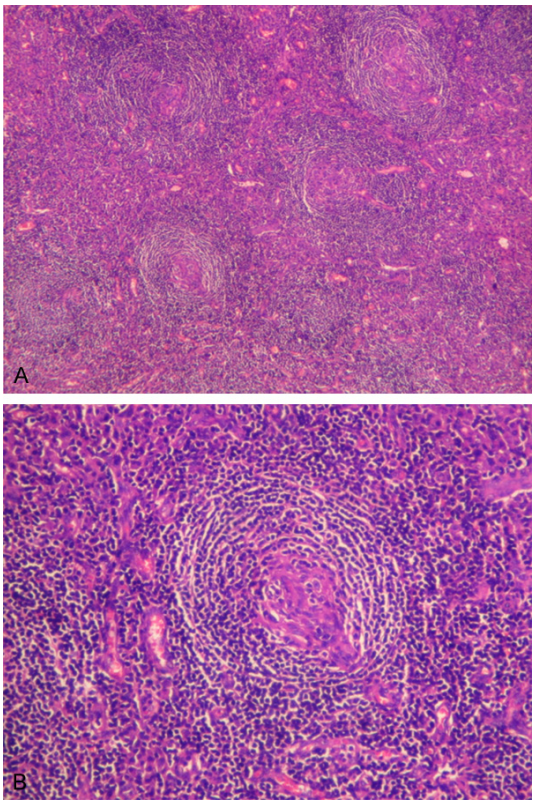

Figure 8. A, B. Histological examinations stained with hematoxylin and eosin revealed lymphoid hyperplasia and plasma cell infiltration, with interfollicular vascularization.

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 diagnosisis an excisional biopsy from the lymph node which retained the diagnosis of muticentric CD in our patient [7]. This entity is thought to comprise several disease entities such as PS [8, 9]. Despiste 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

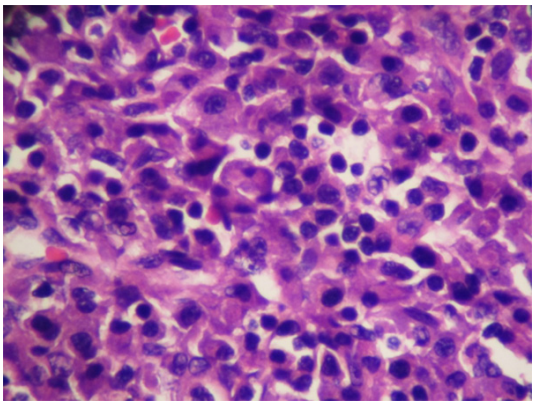

Figure 9. The interfollicular areas showed sheets of mature plasma cells.

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 recomanded 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, itis 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

[1] Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 1956; 9: 822-830.

[2] Cronin DM, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol 2009; 16: 236-246.

[3] Ko SF, Hsieh MJ, Ng SH, Lin JW, Wan YL, Lee TY, Chen WJ, Chen MC. Imaging spectrum of Castleman's disease. AJR Am J Roentgenol 2004; 182: 769-775.

[4] Li J and Zhou DB. New advances in the diagnosis and treatment of POEMS syndrome. Br J Haematol 2013; 161: 303-315.

[5] Baranzelli A, Akkad R, Bouchindhomme B, Tacelli N, Delourme J, Dhalluin X, Lafitte JJ, Scherpereel A, Remy-Jardin M, Cortot AB. Castleman's disease: unusual presentation of Castleman's disease and review of literature. Rev Pneumol Clin 2013; 69: 55-9.

[6] Dispenzieri A. How I treat POEMS syndrome. Blood 2012; 119: 5650-5658.

[7] Cervantes CE, Correa R. Castleman disease: a rare condition with endocrine manifestations. Cureus 2015; 7: e380.

[8] Kojima M, Nakamura S, Nishikawa M, Itoh H, Miyawaki S, Masawa N. Idiopathic multicentric Castleman's disease. A linicopathologic and immunohistochemical study of five cases. Pathol Res Pract 2005; 201: 325-332.

[9] Van Rhee F, Stone K, Szmania S, Barlogie B, Singh Z. Castleman disease in the 21st century: an update on diagnosis, assessment, and therapy. Clin Adv Hematol Oncol 2010; 8: 486-498.

[10] Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. Am J Hematol 2015; 90: 951-62.
[11] Shi X, Hu S, Yu X, Zhuang Q, Luo M, Jiang Q, Wang L, Lu Y, Fei X, Xi X, Zhu Y. Clinicopathologic analysis of POEMS syndrome and related diseases. Clin Lymphoma Myeloma Leuk 2015; 15: e15-21.
[12] Bonekamp D, Hruban RH, Fishman EK. The great mimickers: Castleman disease. Semin Ultrasound CT MR 2014; 35: 263-71.
[13] Goranova-Marinova VS, Chernev KG, Goranov SE. Poems syndrome-a rare variant of plasma cell dyscrasia. Case report and review of literature. Folia Med (Plovdiv) 2009; 51: 5-11.
[14] Li J, Zhang W, Jiao L, Duan MH, Guan HZ, Zhu WG, Tian Z, Zhou DB. Combination of melphalan and dexamethasone for patients with newly diagnosed POEMS syndrome. Blood 2011; 117: 6445-6449.
[15] Szturz P, Adam Z, Rehák Z, Koukalová R, Sprláková-Puková A, Michalka J, Smardová L, Volfová P, Lengerová M, Mayer J. Castleman disease: retrospective single-center study of therapeutic results in 10 patients. Klin Onkol 2013; 26: 124-34.
[16] Adam Z, Pour L, Krejčí M, Zahradová L, Szturz P, Koukalová R, Rehák Z, Nebeský T, Hájek R, Král Z, Mayer J. The effect of lenalidomide on rare blood disorders: langerhans cell histiocytosis, multicentric Castleman disease, POEMS syndrome, Erdheim-Chester disease and angiomatosis. Vnitr Lek 2012; 58: 856-66.
[17] Gracia-Ramos AE, Cruz-Domínguez Mdel P, Vera-Lastra OL. Multicentric hyaline vascular Castleman disease. A POEMS type variant. Rev Med Inst Mex Seguro Soc 2013; 51: 464-7.
[18] Kubokawa I, Yachie A, Hayakawa A, Hirase S, Yamamoto N, Mori T, Yanai T, Takeshima Y, Kyo E, Kageyama G, Nagai H, Uehara K, Kojima M, Iijima K. the first report of adolescent TAFRO syndrome, a unique clinicopathologic variant of multicentric Castleman's disease. BMC Pediatr 2014; 14: 139.