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POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, M PROTEIN, SKIN LESIONS) SYNDROME

A South America's report

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ABSTRACT - The POEMS syndrome, also known as Crow-Fukase syndrome, is an unusual systemic disorder described mainly in Asian individuals. It is characterized by the presence of (P)polyneuropathy, (O)organomegaly, (E)endocrinopathy, (M) M-protein, and (S) skin changes. Several other associated condictions such as sclerotic bone lesions, Castleman disease, low-grade fever, edema and hematologic disorders are usually seen. We describe five Brazilian patients with this syndrome. Two patients presented Castleman disease, one patient presented osteosclerotic myeloma and in two patients no associated conditions were found.

KEY WORDS: peripheral neuropathy, POEMS, monoclonal protein.

POEMS (polineuropatia, organomegalia, endocrinopatia, proteína M, alterações de pele): relato sul-americano

RESUMO - A síndrome POEMS, também conhecida como síndrome de Crow-Fukase é uma desordem sistêmica rara descrita principalmente em asiáticos. Ela é caracterizada pela presença de (P) polineuropatia, (O) organomegalia, (E) endocrinopatia, (M) proteína M e (S) alterações de pele. Diversas outras manifestações, tais como lesões osteoescleróticas, doença de Castleman, febre baixa, edema e distúrbios hematológicos são freqüentemente observados. Apresentamos cinco pacientes brasileiros com esta síndrome. Dois pacientes apresentaram diagnóstico de doença de Castleman, um paciente com mieloma osteoesclerótico e em dois pacientes, nenhuma condição associada foi encontrada.

PALAVRAS-CHAVE: neuropatia periférica, POEMS, proteína monoclonal.

POEMS syndrome (PS), also known as Crow-Fukase syndrome, is an unusual systemic disorder characterized by the presence of (P) polyneuropathy, (O) organomegaly, (E) endocrinopathy, (M) M-protein, and (S) skin changes[1]. It was firstly described by Scheinker in 1938[2], and the acronym POEMS was coined in 1980 by Bardwick et al.[1]. Although the acronym POEMS describes the five more important features of this syndrome, several other manifestations including sclerotic bone lesions, Castleman disease, low-grade fever, infiltrative orbitopathy, finger clubbing, hyperhidrosis, pleural effusion, ascites, edema and hematologic disorders can be seen[3,4]. It has been reported mainly in Japanese individuals, although affected individuals from other ethnic backgrounds have also been described[5]. There is a male/female ratio of 2:1[5,6].

We report five Brazilian non-Asian descendant patients with PS and discuss the clinical aspects and therapeutic options for this syndrome.

CASES

Case 1 – A 33 year- old man was admitted with a history of paresthesias and progressive weakness in lower limbs that resulted in inability to walk, edema and trophic ulcerations in both ankles. The general physical examination showed the presence of skin hyperpigmentation and gynecomastia. The neurological exam showed a right ptosis, distal weakness in the lower limbs, absent deep tendon re-

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flexes, and distal lower limbs hypoestesia. Complete blood cell count, erythrocyte sedimentation rate (ESR) and serum glucose were in normal range. Serologies for HIV, Hepatitis C virus (HCV), Hepatitis B virus (HBV) and VDRL were negative. Serum protein electrophoresis showed an increased gamma spike. An endocrine evaluation disclosed no abnormalities. CT scan revealed a lytic lesion in the frontal bone extending through the right orbit and frontal sinus. Electrophysiological (EMG) studies showed a symmetrical demyelinating polyneuropathy. Bone biopsy was done at the site of the lesion and the histopathological analysis was suggestive of a multiple myeloma. The patient underwent a surgical resection of the bone lesion and, two years later, he had markedly recovered from the neurological symptoms.

Case 2 – A 37 year-old man was admitted due to a 3-year history of progressive back pain, weakness and paresthesias in lower limbs. Two months before the admission, he also developed hyperhidrosis, five-kilogram weight loss and sexual impotence. The general examination showed the presence of small hypercromic lesions in the feet and legs and bilateral axillary and inguinal lymphadenopathy. The neurological exam revealed a distal leg weakness associated with absent deep tendon reflexes bilaterally. No sensory deficits were observed. Laboratory tests showed a normal blood count, ESR, serum glucose and renal function. Urine analysis revealed protein traces, but no Bence Jones' protein was detected. Serologies for HIV, HBV and HCV as well as VDRL were negative. Protein electrophoresis disclosed a monoclonal IgG spike. Rheumatologic tests were negative. Radiographic bone survey showed multiple lesions, with a mixed lytic and sclerotic pattern in the superior diafisis of the left humerus, in the sacrum and femurs. No organomegaly was observed on an abdominal and pelvis CT scan. The cerebrospinal fluid (CSF) presented 1 cell/mm^3 and 98 mg/dL protein. EMG was consistent with a sensorimotor polyneuropathy with mixed axonal and demyelinating features. Biopsy of a left axillary lymphnode was suggestive of Castleman's disease. Sural nerve biopsy demonstrated no signs of inflammation. Semithin transverse sections showed evidence of mild demyelination and signs of axonal degeneration (Fig 1). Fibers with fine myelin were observed in some fascicles, as well as groups with axonal regeneration (Fig 1). The dissociated fiber study demonstrated numerous ovoids of myelin indicating axonal degeneration and rare fibers with short demyelinated segments. These features were suggestive of an axonal neuropathy with signs of secondary demyelination. The patient was lost to follow up.

Case 3 – A 51 year old man presented with a 7 month-history of paresthesias in both upper and lower extremities associated with a 30 kilogram weight loss, sexual impotence and gynecomastia. The general examination showed skin thickening at hands and cervical and inguinal lymphadenopathy. The neurological examination demonstrated an arreflexic tetraparesia associated with amyotrophy in the lower limbs and distal hypoestesia. No cranial nerve deficits were observed. Laboratory tests presented normal

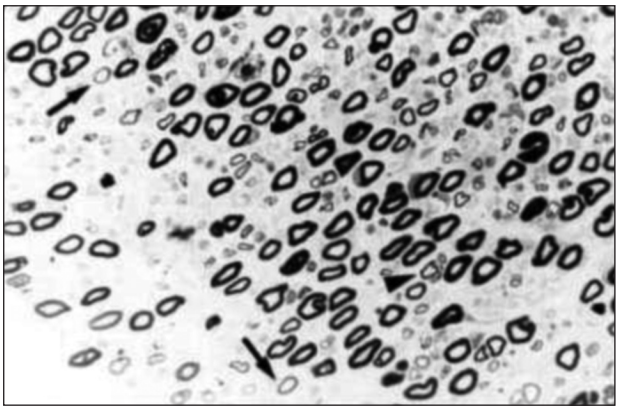

Fig 1. Sural nerve biopsy from Patient 2 showing loss of large and small myelinated fibers. Some fibers present a thin myelin sheet (arrows) Toluidin blue, 40X.

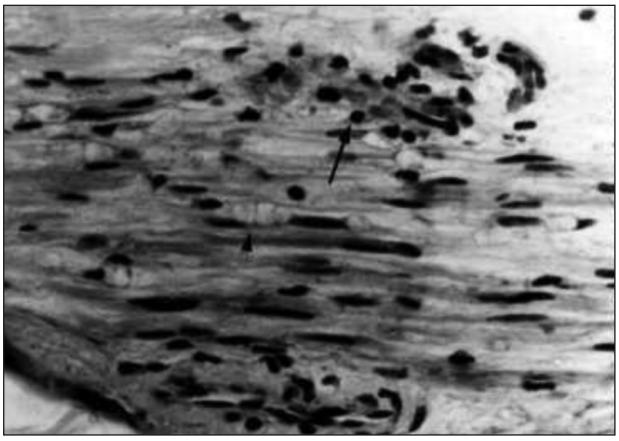

Fig 2. Photomicrograph of sural nerve longitudinal section from Patient 4 showing some mononuclear cells surrounding a small endoneurial vessel. H & E, 40X.

blood count, electrolytes, liver and renal functions. ESR was 115 mm at first hour. Anti nuclear antibodies and rheumatoid factor were negative. The serum protein electrophoresis appeared polyclonal and an immunoelectrophoresis was not done. CSF analysis showed no white cells, increased protein content (129 mg/dL) and normal glucose content. Bone X-ray survey did not reveal abnormalities. CT scan of the abdomen demonstrated hepatosplenomegaly. Biopsy of the cervical ganglion showed hyperplasia consistent with Castleman disease. Bone marrow biopsy was considered normal except for an increased number of plasmocytes (approximately 6%). EMG was consistent with a distal symmetric axonal sensory and motor neuropathy. Melphalan and prednisone were started and the patient was discharged one month later with partial improvement. Two months after, he was admitted again due to anasarca, renal dysfunction and the skin lesions were worse, with a scleroderma like appearance. He refused treatment and left the hospital against medical advice. He was admitted again nine months later with a diagnosis of adrenal insufficiency and died soon after from sepsis.

Case 4 – A 41-year-old man was admitted with an 18-month history of burning dysaesthesias in a "stocking " distribution associated with progressive weakness of the lower limbs. He also developed skin hyperpigmentation, ten-kilogram weight loss and sexual impotence. The general exam showed a diffuse adenomegaly, hepatosplenomegaly and leg edema. The neurologic exam showed a distal symmetric tetraparesia associated with hypotonia, absent deep tendon reflexes and distal lower limb hypoestesia. Protein electrophoresis presented polyclonal pattern. CSF analysis demonstrated a high protein content (240 mg/dL), with normal cell count and glucose content. Serologic tests for *Toxoplasma gondii*, HSV, CMV, HTLV-1 and HIV as well as VDRL were negative. Radiographic bone survey demonstrated a single osteosclerotic lesion in iliac bone on the left side. EMG showed a demyelinating sensorimotor polyneuropathy. Sural nerve biopsy presented small foci of mononuclear cells (lymphocytes and plasmocytes) in the endoneurium and vessels of the subperineurium (Fig 2). A moderate fibrosis in the epineurium and loss of myelinic fibers were noticed. No amyloid deposits were observed. Teased- fiber preparations showed an intense loss of myelin in fibers of all sizes and axonal degeneration. Extensive endoneurial edema was present. These features were consistent with a chronic predominantly axonal inflammatory neuropathy. Unfortunately no follow up information was available since the patient move to another city.

Case 5 – A 31-year-old male presented with a tetraparesia associated with a 15-kilogram weight loss, diffuse skin hyperpigmentation, hypertrichosis, and sexual impotence. On general examination, there were gynecomastia, anasarca, cervical and axillary adenomegaly and testicular atrophy. The neurological examination showed a distal symmetric tetraparesia with absent deep tendon reflexes. CSF analysis disclosed no abnormalities. Protein electrophore-

Table. Clinical characteristics of five cases.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Polyneuropathy					
Peripheral neuropathy	+	+	+	+	+
Papilledema	–	–	+	–	–
Cerebrospinal fluid protein above 50 mg/dL	ND	+	+	+	–
Organomegaly					
Hepatomegaly	–	–	+	+	–
Splenomegaly	–	–	+	+	–
Lymphadenopathy	–	+	+	+	+
Castleman disease	–	+	+	–	+
Endocrinopathy					
Gynecomastia	+	–	+	–	+
Sexual impotence	–	+	+	+	+
Hypoadrenalism	–	–	+	–	–
M component					
Monoclonal protein	–	+ (IgG)	–	–	+ (IgG)
Policlonal protein	–	–	+	+	–
Abnormal protein electrophoresis	+	–	–	–	–
Skin changes					
Hyperpigmentation	+	+	+	+	+
Hypertrichosis	–	–	–	–	+
Thickening	–	–	+	–	–
Extravascular volume overload					
Peripheral edema	+	–	+	+	+
Ascites	–	–	+	–	–
Pleural effusion	–	–	–	–	–
Bone lesions					
Sclerotic only	–	–	–	+	–
Lytic only	+	–	–	–	–
Mixed sclerotic and lytic	–	+	–	–	–
Other features					
Weight loss > 5 kilograms	–	+	+	+	+
Thrombocytosis	–	–	–	+	–
Polycythemia	–	+	–	–	–
ESR > 30mm at 1st hour	–	–	+	–	–
Hyperhydrosis	–	+	–	–	–

+, present; –, Absent; ND, not done; >, more than.

sis showed a monoclonal IgG spike, but there was no Bence Jones protein. Radiographic bone survey disclosed no lesions. Electrodiagnostic study disclosed reduction of sensory and motor action potentials with positive sharp waves and fibrillations in distal muscles consistent with an axonal polyneuropathy. Adenomegaly was observed on abdominal CT scan. Bone marrow biopsy disclosed no abnormalities. Biopsy of a lymph node showed angiofollicular lymphoid lesion and sural nerve biopsy demonstrated loos of myelinated fibers and axonal degeneration. A diagnosis of POEMS was made and the patient was treated with Melphalan and prednisone. The patient gradually improved from the weakness and the endocrine manifestations.

The clinical findings in the five cases are summarized in Table.

All of the patients gave their informed consent prior to their inclusion in the study.

DISCUSSION

All patients in this study were men and the mean age at onset was 37.8 years (range 31-51 years). There is a male preponderance of POEMS syndrome as reported in Asian series as well as other South-American cases. In a review of 102 Japanese cases, the mean age at onset was 46 years[6].

Evidence of a peripheral neuropathy was present in all five patients at the time of the first evaluation. Neuropathic symptoms are the presenting feature in most of the individuals and its considered as requirement for the diagnosis of POEMS[2]. Distal symmetric sensory loss, absence of the deep tendon reflexes and progressive ascending weakness usually overshadowing the sensory symptoms are frequently seen[2]. EMG findings include slowing of nerve conduction velocities predominantly in the intermediate nerve segments. Conduction block are rare. Decreased compound muscle action potentials are typically observed in the lower than the upper limbs as seen in our cases[7].

Autonomic dysfunction such a bradycardia and sphincterial disorders and cranial nerve involvement are rarely seen. Patient 5 developed a syncopal state with palmoplantar sweating in absence of adrenal insuficiency, suggesting an autonomic component. CSF protein concentration was increased in three patients as previously described[6].

A sural nerve biopsy was performed in three patients. Histological analysis evidenced of a chronic inflammatory axonal neuropathy with demyelinating findings. Both axonal and demyelinating lesions have been described in association with POEMS[8]. The endoneurial edema, as seen in Case 4, points toward an alteration in the blood-nerve barrier considered by Koike and Sobue[8]. A major difference between POEMS syndrome and the IgM neuropathies is that, in the first one, immunoglobulin deposits are hardly ever seen[2].

Organomegaly (hepatomegaly, splenomegaly and/or adenomegaly) is present in 50-78% of the affected individuals in different series[2,5,6]. Liver and spleen enlargement are usually associated with normal histological findings. However Castleman's disease is frequently diagnosed in patients with POEMS and adenomegaly[5]. In our study, all but one patient had organomegaly and three were diagnosed with Castleman's disease.

A monoclonal plasmaproliferative disorder was present in two out of five patients (patients 2 and 5). Two additional patients had a protein electrophoresis with a polyclonal pattern (patients 3 and 4). Immunofixation is more sensitive than the serum protein electrophoresis to the detection of a monoclonal protein[2]. Unfortunately, the first method was not available. This could explain the absence of a monoclonal spike in three patients. All patients had evidence of an endocrinopathy at time of diagnosis. Clinical evidence of gonadal axis dysfunction was observed in all five cases, although this was not confirmed by laboratorial data. This could be explained by either an absolute hyperestrogenemia or a relative one in a setting of hypoandrogenism. One patient developed adrenal insufficiency later in the course of the disease. It is an uncommon feature, being reported in 16% of the patients in the series of Dispenzieri et al.[2]. Interestingly, none of the individuals in our study had evidence of thyroid dysfunction or diabetes mellitus.

Skin changes associated to PS are characterized by thickening, hypertricosis, hyperpigmentation, clubbing, skin angiomas, acrocyanosis, plethora and white nails[3]. The most common cutaneous lesion is hyperpigmentation[2], which can be diffuse or localized and is unrelated to adrenal insufficiency[5]. It was seen in all individuals at the time of first evaluation. Hypertrichosis and skin thickening were present in one patient each (patients 5 and 3, respectively).

The classic pattern of the bone lesions in POEMS is a sclerotic or mixed sclerotic and lytic. They can be solitary or multiple. Exclusively lytic lesions are seen just in a small proportion of the patients[2]. According to Soubrier et al.[5] prognosis is better for solitary bone lesions, but this was not confirmed in a recent larger series[2].

Extravascular volume overload is a less recognized aspect of the POEMS, although it is present in a great

percentage of the affected individuals[6]. Four out of five patients in this series had peripheral edema or ascites either at presentation or during the course of disease. Its pathogenesis is not fully understood but there is evidence of a systemic disturbance of the vascular permeability[5].

There are several other manifestations that have been observed in association with POEMS. Hyperhidrosis, polycythemia, thrombocytosis and elevated ESR were present in one patient each (Table). Weight loss greater than five kilograms was common being reported in all except one of our patients.

The pathogenesis of this condition is not fully understood. Several pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor have been implicated in the development of the POEMS[9-11]. Koike and Sobue suggest that the vascular endothelial growth factor (VEGF), which is probably secreted by plasma cells, can also be implicated, since it induces a reversible and rapid increase in the vascular permeability and is a growth factor for endothelial cells[8].

Several treatment strategies have been used in POEMS syndrome. Solitary bone lesions have been treated with radiation or surgical removal with improvement of both systemic and neurologic symptoms[5]. For patients with diffuse or no bone lesions, corticosteroids, alkylators, interferon alfa and azathioprine, intravenous immunoglobulin, or plasmapheresis should be considered[12]. In a recent report, 14 out of 16 patients with POEMS submitted to peripheral blood stem cell transplant had neurologic improvement or stabilization[13]. The response to treatment and survival is not dependent of the number of the POEMS features[2].

To summarize, we presented the largest series of South American patients with POEMS and reviewed the clinical and laboratorial features of this disease. This rare syndrome should be included in the differential diagnosis of acquired neuropathies associated with multisystemic manifestations.

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