Case Report

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Primary Diffuse Large B-Cell Lymphoma with Features Simulating POEMS Syndrome: Case Report and Review Of The Literature

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Abstract

POEMS syndrome is a rare systemic affection of paraneoplastic origins. The main manifestations include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. This disease is commonly associated with plasma cell dyscrasia or Castleman disease. A 51-year-old-man presented with a four-month history of gait impairment, four-limb sensorimotor deficit, general areflexia and facial diplegia. The diagnosis of chronic polyradiculoneuritis was made based on Cerebrospinal fluid (CSF) analysis and electromyography study (EMG). At the time of initial evaluation, physical examination displayed enlarged lymph nodes, hepatosplenomegaly, endocrinopathy and skin changes. Complete Blood Count did not reveal significant monoclonal plasma cell proliferative disorder. The biopsy of the adenopathy identified a large B-cell lymphoma. We concluded a POEMS-like syndrome due to the lack of monoclonal plasma cell proliferative disorder. To our knowledge, this is the third reported case of B-cell Lymphoma associated with POEMS features. Our findings may suggest that POEMS syndrome has an unusual presentation in patients with diffuse large B-cell lymphoma even in the absence of monoclonal plasma cell proliferative disorder considered as the essential criterion.

Keywords: POEMS syndrome; B-cell lymphoma; Monoclonal Gammapathy of Undetermined Significance; Polyneuropathy.

Introduction

POEMS syndrome is a rare systemic affection of paraneoplastic origins. The main manifestations include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. This disease is commonly associated with plasma cell dyscrasiaor Castleman disease [1]. According to the World Health Organization (WHO), diffuse large B-cell lymphomas are classified as a distinct lymphoma entityandre present the most frequent group of non-Hodgkin's lymphomas (NHL) in adults including various groups of lymphoid neoplasms with heterogeneous clinical, histological, immunophenotypic, cytogenetic and molecular features[2]. The association of POEMS syndrome with diffuse large B-cell lymphoma is rare and we found two cases of association between primary cutaneous large B-cell lymphoma and POEMS. We report a rare case of an atypical POEMS syndrome with diffuse large B-cell non-Hodgkin's lymphoma, through which we highlight unusual features that may be considered in future diagnostic criteria.

Case Report

A 51-year-old man developed facial diplegia, numbness and weakness of 4 limbs and gait impairment. Two weeks later, he developed rapidly progressive bilateral swelling in the cervical, axillary and inguinal regions with gradually worsening instability when walking. He was therefore admitted to our hospital.

Physical examination revealed bilateral, painless lymphadenopathy in the retro auricular, cervical, occipital, axillary and inguinal regions with hepatosplenomegaly. Neurological examination found tetraparesis (3/5 according to the manual muscle testing), general are flexia, symmetric facial diplegia and loss of proprioception in lower limbs. Hyperpigmentation was noted in the left lower limb associated to an oval-shaped nodular lesion with a purple smooth surface and a firm consistency on the right shoulder **(Figure 1)**.

Results

LAB analysis revealed the following results: blood cell count (CBC): white blood cells= 6.12 × 109.L-1[69.9% neutrophils,

14.2% lymphocytes]; hemoglobin= 143 g.L-1; platelet =189 × 109 elm.L-1; sodium= 125 mmol.L-1; calcium= 2.32 mmol.L-1; total protein= 70g L-1; creatinine= 51µmol.L-1; albumin= 37.2 g L-1; LDH = 372 IU L-1; CRP= 17 mg.L-1.

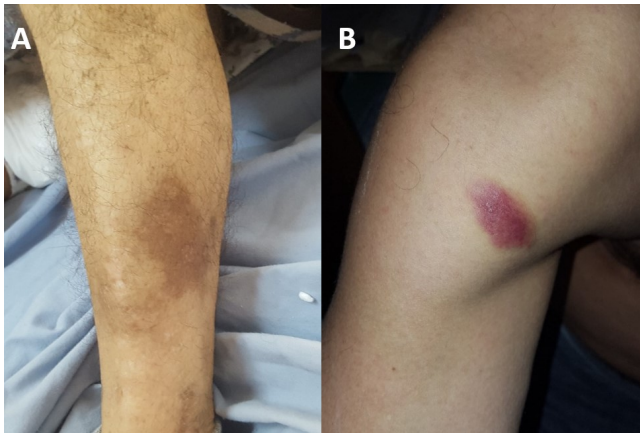

Figure 1: Patient's cutaneous manifestation: (A)Clinical observation of the hyperpigmentation in the left lower limb. (B)Clinical observation of the nodular lesion on the right shoulder.

Endocrine investigations showed hypothyroidism: TSH=5.432; T4=0.7. Protein electrophoresis revealed an increase in Beta-2 Globulin with a monoclonal immunoglobulin Mkappa (IgMκ) paraprotein spike (6.6g.L-1) **(Figure 2)**.

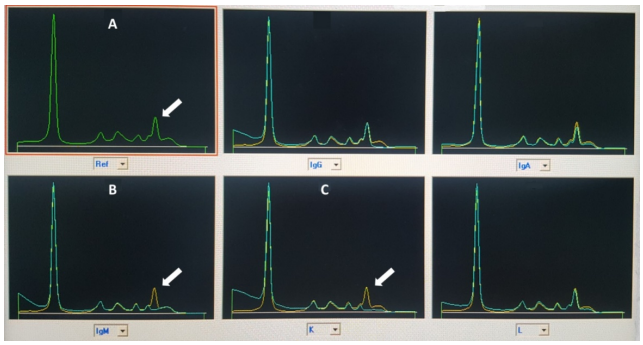

Figure 2: Capillary electrophoresis and immunosubtraction of patient'sserum: arrow A shows the spike in Beta-2 Globulin fraction. Arrows B and C show the difference between the sample analyzed before and after immunosubtraction.

Bone marrow smear was infiltrated by 9% of plasma cells with few signs of dysmorphia (2% of plasmablasts).

Computed Tomography scans revealed enlarged cervical, axillary thoracic, abdominal and inguinal lymph nodes, and hepatosplenomegaly. No lytic bone lesion was found.

Nerve conduction studies (NCS) were performed using standard surface stimulation and recording techniques. Compound muscle action potentials (CMAPs) were evaluated at the bilateral peroneal (extensor digitorum brevis and Tibialis anterior), tibial (abductor hallucis), median (abductor pollicis brevis), and ulnar (adductor minimi) nerves. Motor conduction velocities (MCVs) were evaluated from the wrist to the elbow for the upper limb nerves, and from the ankle to the knee for the lower limb nerves. Sensory nerve action potentials (SNAPs) were recorded from the median and ulnar nerves via orthodromic studies and from the sural and superficial fibular nerves via antidromic studies.

The nerve conduction study showed the absence of a response in both distal peroneal stimulation (extensor digitorum brevis), great reduction in both the upper (ulnar) and lower limbs (peroneal and tibial) CMAPs, prolongation in distal motor latency in the right median and both tibial nerves, the absence of SNAPs in ulnar, median and superficial fibular nerves, normal SNAPs in radial and sural nerves and absence of conduction block. The NCS parameters are shown in **Table 1 and Table 2**.

Table 1: Motor Nerve conduction study findings in our patient.

Nerve / Site	Latence (ms)	Amplitude (mv)	NCV(m/s)
Median (right)			
Wrist	4.7	7.4	
Elbow	9.8	6.8	44.3
Ulnar (right)			
Wrist	2.8	1.1	
Elbow	-	-	-
Peroneal (left / Tibialis anterior)			
Below Fibular head	5.7	0.5	
AboveFibularhead	19.7	0.28	16.4
Peroneal (right/ Tibialis anterior)			
Below Fibular head	7.6	1.1	
AboveFibularhead	14.1	0.3	12.3
Tibial			
Ankle	6.8	1.1	-
Tibial			
Ankle	9.1	0.3	-

According to these findings, the diagnosis of a sensorimotor polyneuropathy with a pattern of diffuse axonal degeneration and demyelination was made.

A biopsy of the right neck lymph node showed loss of normal architecture with diffuse infiltration composed of large lymphoma cells with narrow cytoplasm, round vesicular nuclei with prominent nucleoli. Nuclear pleomorphism and numerous mitotic cells were observed. Immunohistochemical study revealed that the lymphoma cells were positive for CD20 and CD3, and a high expression of Ki67 (70%). Contrariwise, they were negative for CD30 **(Figure 3)**. Biopsy of the

cutaneous lesion of the right shoulder concluded to a cutaneous localization of the large B-cell lymphoma **(Figure 4)**.

Table 2: Sensory Nerve conduction study findings in our patient.

Nerve / Site	Latence (ms)	Amplitude (uv)	NCV (m/s)
Median (right) 2nd digit	-	NR	-
Ulnar (right) 5th digit	-	NR	-
Radial Forearm	1.9	14.7	41.7
Superficial fibular-Leg	-	-	-
superficial fibular-Leg	-	-	-
Sural (right) Leg	6.8	9.4	-
Sural (left) Leg	9.1	11.2	-

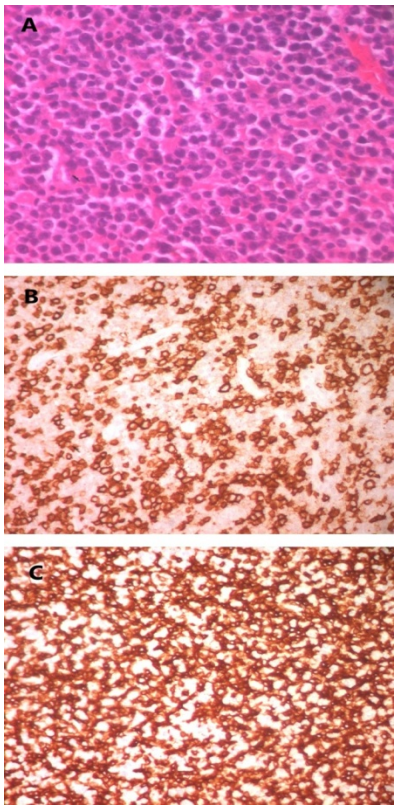

Figure 3: Biopsied adenopathy. (A): large lymphoma cells with narrow cytoplasm, round vesicular nuclei with prominent nucleoli (Hematoxylin – eosin stain; original magnification ×200). (B): Lymphoma cells positive for CD20 (original magnification ×200).(C): Lymphoma cells positive for CD3 (original magnification ×200).

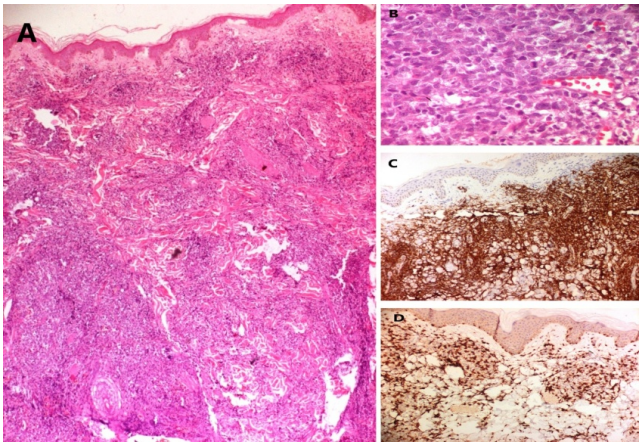

Figure 4: Biopsied cutaneous shoulder lesion. (A): diffuse infiltration of dermis and subcutaneous tissue by neoplastic cells. A clear grenz zone is seen separating lymphoma cells from epidermis (Hematoxylin – eosin stain; original magnification ×40). (B): large lymphoma cells with narrow cytoplasm, round vesicular nuclei with prominent nucleoli (Hematoxylin–eosin stain; original magnification ×200). (C): Lymphoma cells positive for CD20 (original magnification ×200). (D): Lymphoma cells positive for CD3 (original magnification ×200).

Our results are consistent with a Diffuse large B-cell lymphoma (DLBCL) with cutaneous metastasis [3]. Moreover, the patient manifested many signs and symptoms characteristic of POEMS syndrome such as polyneuropathy, endocrinopathy, skin changes and organomegaly. Although monoclonal plasmacell proliferative disorder is required for the diagnosis ofPOEMS syndrome, the patient was instead diagnosed with POEMS-like syndrome associated to a DLBCL [1,4].The serum paraprotein was classified as monoclonal gammopathy of undetermined significance (MGUS). After six courses of R-CHOP therapy (a regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) the lymphadenopathy disappeared **(Figure 5)** and neurological symptoms improved markedly.

Discussion

The first description of POEMS syndrome was established in 1938 by Scheinker, who reported the case of a 39-year old man who had a solitary plasmacytoma with polyneuropathy and cutaneous changes [5]. Later on, more cases have been reported by Crow (1956) and Fukase (1968). It was then known as Crow-Fukase syndrome [6] or Takatsuki syndrome [7]. Acronym POEMS was proposed in 1980 by Bardwick [8]. It characterized the syndrome by the combination of polyneuropathy (P), organomegaly (O), endocrinology (E), monoclonal protein (M) and skin changes (S).Other features, not included in the acronym, may exist such as papilledema, extravascular volume overload, sclerotic bone lesions, thrombocytosis, erythrocytosis, elevated VEGF levels,

abnormal pulmonary function tests or a Castleman disease [1,4].

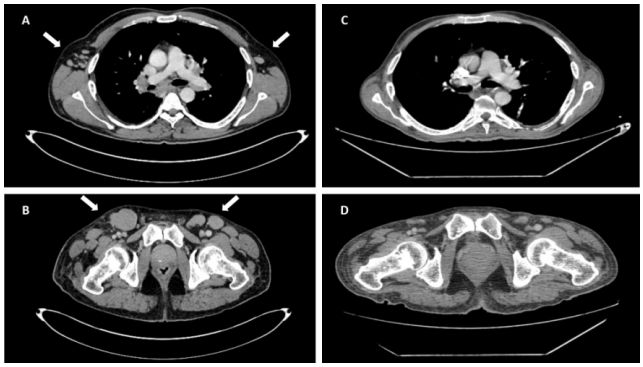

Figure 5: Pre and post-therapy thoraco-abdominopelvic computerized tomography (CT).Pre-therapy CTshowsenlarged bilateral infraclavicular (A) and inguinal (B) lymph nodes. They disappear after 6 courses of R-CHOP therapy (C and D) on post-therapy CT.

The mechanisms responsible for the syndrome's various clinical manifestations are not yet known. A close correlation between the symptoms of POEMS syndrome and elevated circulating levels of various cytokines, including VEGF, IL-6 and IL-12, has been suggested [9-11].Up to date, VEGF is the cytokine that correlates best with this disease activity [12]. However, the mixed results of anti-VEGF therapy suggested that it may not be the driving force of the disease [13,14]. Now, it is widely accepted that VEGF is probably a downstream mediator of a paraneoplastic syndrome rather the pathogenic initiating factor [15]. The type of cells secreting these cytokines is still unknown, however, it may be attributed to an outgrowth of plasma cells since POEMS syndrome is often accompanied by plasmacytoma. The presence of high amount of plasma cells in our patient is consistent with this theory.

Due to the lack of pathognomonic sign or specific test, diagnostic of POEMS syndrome is based on the association of clinical findings, but general consensus is yet to be reached. The number of clinical features needed for the diagnosis is ambiguous. Therefore, the minimal criteria along with the major criteria required for the diagnosis of POEMS syndrome, based on a retrospective review of a single institution's experience, were defined [1,4,16]. Polyneuropathy and monoclonal plasma cell proliferative disorder are both mandatory criteria. However, cases of POEMS syndrome cases without monoclonal plasma cell proliferative disorder or Castleman disease have been reported [6,7,17,18], which raises questions about considering this as mandatory for definite diagnosis.

The association of POEMS syndrome with diffuse large B-cell lymphoma is rare. We reported 2 cases of B-cell lymphoma associated with POEMS syndrome or POEMS features. The first was primary cutaneous large B-cell lymphoma, leg type, with POEMS-like syndrome [19]; and the second was a DLBCL associated with POEMS syndrome [20]. B-cells, which are precursors of plasma cells, might be implicated in the process of initiating the POEMS syndrome since they are a possible source of VEGF [21].

Another particularity of our case is the nature of the M component (IgMκ). In large series, Nakanichi *et al.* (1984) reported IgM in one of 75patients (1.3%) and kappa light chain in 4 (3 IgA; 1 IgG) patients (5%) [6]. Dispenzieriand colleagues (2002) reported IgM in 1 of 84 patients (1.2%) and lambda light chain in all of their patients [4]. No IgM or kappa light chain were reported in the French series [18]. In the literature, only 2 cases of IgMκ associated to POEMS syndrome were reported, both of them were associated to Waldenström's macroglobulinemia [22,23].These cases suggested that IgM might have a role in the geneses of POEMS syndrome and that Lambda light chain was not necessary for its development.

In most of paraneoplastic syndromes, the main goal of treatment is to control the tumor. To treat our patient, we used R-CHOP combination that is the backbone of DLBCL therapy, with a 10-year progression free survival at 36.5% [24,25].In typical POEMS syndrome, treatment protocols are based on the therapeutic arsenal of plasma cell disorders like multiple myeloma. Initial improvement is always obtained, but long-term follow-up studies have yet to be published [16].

Conclusion

In summary, our study reported a rare POEMS-like syndrome with DLBCL and IgM kappa. We suggested that B-Cell lymphoma might be associated to POEMS features. Therefore, monoclonal plasma cell proliferative disorder or Castleman Disease should be reconsidered as mandatory criterion in POEMS syndrome. Moreover, physicians should be aware of the possible role of B-cells and IgM-κ in the geneses of this disease.

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