Endocrinopathy in polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome

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Abstract

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome is a rare paraneoplastic syndrome due to underlying plasma cell disorder. It belongs to group of plasma cell dyscrasias such as multiple myeloma, waldenstrom's macroglobulinemia, castleman disease and monoclonal gammopathy of undetermined significance. The term POEMS syndrome was first coined in 1980 by Bardwick. In the last 10 years clinical criteria to diagnose POEMS syndrome have been elaborated to avoid overlap with other haematological disorders. Due to disease rarity there is very few case series and case reports described in literature. This is a haematological disease which frequently presents with peripheral neuropathy but endocrine dysfunction can be a presenting or an associated feature. We report two cases of POEMS syndrome who presented with endocrinopathy as a predominant feature with literature review of this syndrome.

Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare medical syndrome. It begins in middle age and the average age at onset is around 50. It affects up to twice as many men as women.¹ Endocrinopathy can be the main presenting

feature of POEMS syndrome. Most information regarding endocrinopathy in POEMS syndrome has come from isolated case reports and small case series. Specific endocrine abnormalities associated with POEMS syndrome vary from case to case. The cause of endocrinopathy in this disorder is unknown. Involved endocrine organs have been found to be structurally normal suggesting that it may be a functional problem.² Hormonal disorders associated with POEMS syndrome include hypogonadism, diabetes mellitus, hypothyroidism, hyperprolactinemia, Acromegaly, adrenal insufficiency, gynaecomastia in men and hypoparathyroidism.^{3,4}

Case Report #1

A 56 year old Caucasian male was referred to Urology with history of hematuria. He was recently diagnosed with Type 2 Diabetes Mellitus and was treated with oral hypoglycemics. He had history of back ache and pain in his feet for the last 2 years. The pain in his feet was burning in sensation and interfered with his sleep. He had undergone partial thyroidectomy 30 years ago for a large goitre. His imaging showed a renal mass in the lower pole of left kidney and an incidental 5 cm left adrenal mass with enlarged lymphnodes (Figure 1). He was referred to Endocrinologist for evaluation of the left adrenal mass. On examination he was noticed to have hyperpigmented skin on his abdomen (Figure 2) but no haemangiomas were seen. His blood pressure was 140/80 mmHg. His 24 hours urinary metanephrines were markedly high. His laboratory data is shown in Tables 1 and 2. His MIBG Scan showed a focus of increased tracer uptake lying in the left upper quadrant consistent with left sided pheochromocytoma (Figure 3). He had left nephrectomy and adrenalectomy after appropriate preparation. The left renal mass on histology was a myelofibroblastic tumour (Figure 4) and the left adrenal mass was a pheochromocytoma with ganglioneuromatous areas (Figure 5). The removed lymph nodes showed features typical of Castleman's disease of the plasma cell form (Figure 6). His diabetes resolved after removal of pheochromocytoma and he has not required any treatment for diabetes for last 2 years. He had MRI of his spine that demonstrated marked thickening of the nerve roots within the foramina of the right L3/4 and L4/5 levels and left L3/4 levels. There was also extensive plaque like thickening in the soft tissue, at the back, with prominent vessels, and local subcutaneous changes dorsally. There were no osteolytic bone lesions. His nerve conduction study showed axonal neuropathy. He had further work up for Castleman's disease including pro-

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tein studies, bone marrow aspirate and Trephe and CT scan of chest and abdomen. His investigations showed IgG lambda paraproteinemia of 9 gms/L with normal IgA and IgM levels. His full blood count white cell differential, haemoglobin and platelet counts were within the normal range. His bone marrow aspirate was hypocellular with no abnormal infiltrate; cytogenetics demonstrated a normal karyotype: 46,XY with no clonal abnormalities detected. Fifteen cells were analysed. Histology showed a fragmented and hypocellular (25-30%) bone marrow trephine of adequate length. All three cell lines are present with tri-lineage haematopoiesis and good maturation. Immunohistochemical staining showed a mild plasma cell infiltrate (<5% of TNC) with no light chain restriction. There were also scattered B- and T-cells as part of the normal marrow components. No amyloid was seen on congo red staining. Reticulin staining was increased (grade 1-2). The appearances were non-diagnostic and were those of a reactive bone marrow.

He was treated with Rituximab 375 mg/m² on Day 1, 8, 15 and 22, further Rituximab 100 mg a day on Day 1-28, Thalidomide 0.75 mg/kg

orally on Day 1-7 and Prednisolone for Castleman disease. A year later he presented with enlarging thyroid with symptoms of tracheal compression and required total thyroidectomy. He developed hypothyroidism and hyperparathyroidism after the surgery and is now on replacement.

Case Report #2

A 73 year man presented with fatigue and severe leg pains of nearly 6 months duration. He had history of Acromegaly diagnosed at the age of 51 years. This was treated with transphenoidal surgery. He did not receive radiotherapy. His acromegaly was not well controlled so he had treatment with somatostatin analogue and this resulted in remission of his acromegaly. His bilateral leg pain was found to be due to Axonal neuropathy. He was treated with amitriptyline and then pregabalin. He had history of treatment for Pulmonary Tuberculosis in the past. During his follow-up he was found to have mild anaemia. He had high total protein and an elevated ESR. He had Bone aspiration. He had elevated IgM and IgA kappa chain paraproteins and diagnosis of monoclonal gammopathy of unknown significance (MGUS) was made by the haematologist. He has been recently diagnosed with primary Hypothyroidism due to hashimotos thyroiditis. He had no skin pigmentation or haemangiomas. His vascular endothelial growth factor (VEGF) levels were normal at 91 pg/mL (normal less than 771).

Discussion

POEMS syndrome is rare and research in last 10 years has provided more insight in to this multisystem disorder. There are now clear guidelines to diagnose POEMS syndrome;

these include major and minor criteria. In order to make the diagnosis of POEMS syndrome two major and a minor criteria are essential to differentiate this from other haematological conditions like Myeloma, primary systemic amyloidosis and waldenstrom disease. The major criteria include polyneuropathy (typically demyelinating), monoclonal plasma cell proliferative disorder, castleman disease, sclerotic bone disease and elevated VEGF. The minor criteria include organomegaly, extravascular volume overload (pleural effusion, ascites, edema), endocrinopathy, polycythemia, papilledema and skin changes (hyperpigmentation, hypertrichosis, plethora, acrocyanosis, flushing, white nails). Some may have associated symptoms and signs like clubbing, weight loss,

hyperhidrosis and restrictive lung disease.⁵

The endocrinopathies are being recognised more as a part of this syndrome. Thus prevalence of endocrinopathy depends on the timing of the case series of POEMS syndrome. The exact pathogenesis of endocrinopathy is unknown. Initially it was suggested that high prevalence of gamma light chains had a key role in pathogenesis but later studies that included histopathological review of affected organs did not support this hypothesis. No circulating antibodies against the hormone or the hormonal receptor have been found.² Loss of balance between proinflammatory and anti-inflammatory cytokines has been postulated by some research group.⁶ Recently role of vascular endothelial growth factor (VEGF) on neovascularisation and vessel permeability was

Table 1. Clinical characteristics.

	Case 1	Case 2
Age	56	72
Sex	Male	Male
Ethnic origin	Caucasian	Caucasian
Criteria for the diagnosis of POEMS syndrome	4	3
Polyneuropathy	yes	yes
Skin hyperpigmentation	yes	no
Castleman disease	yes	No
Paraproteinemia	no IgG kappa	Yes
Endocrinopathy	yes	Yes
Adrenal	Pheochromocytoma	No
Pituitary	No	Acromegaly
Thyroid	Goitre with retrosternal extension	Hypothyroidism
Diabetes	Yes	No
Albumin	42 g/dL (35-48)	37 g/dL (35-48)
Creatinine	127 umol/L (60-110)	105 umol/L (60-110)
Hemoglobin	12.4 g/dL (13-18)	12.5 g/dL (13-15)
ESR	81 mm/h (1-20)	56 mm/h (1-20)

POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes; ESR, erythrocyte sedimentation rate.

Table 2. Laboratory data.

	Case 1	Case 2
Adrenal	24 hours urine Noradrenaline total urine 1663 nmol/24H (0-500) Adrenaline total urine 729 nmol/24 H (0-100) Dopamine total urine 4739 nmol/24H (0-3000) Normetadrenaline total urine 16.48 umol/24H (0-2.5) Metadrenaline 21.03 umol/24H (0-1.2)	
Acromegaly treated with transphenoidal surgery in 1982		IGF-1 21.1 nmol/L (7.2-21.6) on somatostatin analogue
Free T4	11.9 pmol/L (10-23) on thyroxine 150 mcg	14.4 pmol/L (11-23) on thyroxine 75 mcg
Testosterone	17.3 nmol/L (9.9-27.8)	12.5 nmol/L (9.9-27.8)
FSH	12.3 IU/L (1-10)	7.0 IU/L (1-10)
LH	8.4 IU/L (1-9)	1.4 IU/L (1-9)
Prolactin	176 mU/L (86-324)	139 mU/L (86-324)

FSH, follicle stimulating hormone; LH, luteinizing hormone.

suggested as an etiology.⁷ Goth *et al.* reported increased level of VEGF in patients affected with POEMS syndrome. VEGF expression in blood vessels can be induced by hypoxia and VEGF plays a key role in endothelial cell proliferation, migration and angiogenesis. Over expression of the VEGF in patients with POEMS syndrome is thought to affect several endocrine axes due to disruption of local balance of angiogenic factors which are essential for regulation of hormonal secretion.⁸

Figure 1. Adrenal and renal tumor on magnetic resonance imaging scan.

Figure 2. Hyperpigmented skin rash.

Figure 3. Positive MIBG scan for Pheochromocytoma.

High prevalence of diabetes and hypothyroidism in general population make these insufficient to meet minor criteria for POEMS syndrome but if these develop months to years after the onset of at least one other feature of POEMS syndrome then these could be considered as minor criteria. Hypogonadism is the commonest endocrine dysfunction reported in most case studies. In Mayo series published in 2007, 77% had low free testosterone and 61% had erectile dysfunction.² In a Japanese case

series, 39 of 50 men reported erectile dysfunction,⁹ whereas in the case series from France 9 of 19 men tested had hypogonadism.¹ Hypogonadism is generally secondary in patients with POEMS syndrome and men may present with gynaecomastia in up to 40% of patients with hypogonadism.^{2,10} Hypogonadism may improve after treatment with corticosteroids in POEMS syndrome.¹¹ Both of our patients had normal gonadotropin and testosterone level.

In Mayo series 10 of the 35 patients had elevated prolactin as compared to 4 out of 17 in the French series. The levels are usually mildly elevated as in our first case. Irregular periods and galactorrhea due to elevated prolactin in POEMS syndrome has been reported in women. Hypogonadism in patients with hyperprolactinemia persists even after normalising the prolactin. Treating hypothyroidism does not normalise prolactin in such cases.²

Involvement of thyroid axis is the second most common endocrine manifestation reported in POEMS syndrome. Hypothyroidism is the commonest presentation and it is usually mild. It is also essential rule out autoimmunity as a cause of thyroid illness. 58% of the patients in Mayo series had hypothyroidism with half of them being subclinical. In French series 45% of the cases were hypothyroid. Interestingly 2 out of the 10 patients from French series had secondary hypothyroidism. Antibody binding activity targeting endocrine tissue has been demonstrated in POEMS syndrome.¹² Our first case developed a large goitre causing obstructive symptom and required thyroidectomy though he was clinically and biochemically euthyroid. Our second case developed primary hypothyroidism. This suggests the importance of regular endocrine follow up in patients with POEMS syndrome as manifestations may appear later and may be multiple.

Abnormal glucose metabolism is also a common manifestation in POEMS syndrome. 48% of the patients in Mayo series had abnormal glucose metabolism. 16 had impaired glucose tolerance test (IGT) and 8 had diabetes mellitus (WHO criteria). In French series 40% had abnormal glucose metabolism and similar result of 41% were reported in Japanese series. Patients with diabetes have modest insulin requirements.^{1,2,9} Our first patient had IGT at presentation but after adrenalectomy his oral glucose tolerance has been normal.

Adrenal involvement in POEMS syndrome is infrequent and commonest adrenal disorder is adrenal insufficiency. Majority of the case reports have noted primary adrenal insufficiency. It is not clear if these patients were tested for adrenal autoantibodies.¹³ In Mayo series 6 of the 9 tested with short synacthen test had adrenal insufficiency. Pheochromocytoma in POEMS syndrome has been described in association with neurofibromato-

Figure 4. Myelofibroblastic tumor: the tumor has a patchy mixed inflammatory cell population which in some areas shows numerous plasma cells. The histological appearances support a diagnosis of myelofibroblastic tumor.

Figure 5. Pheochromocytoma with ganglioneuromatous areas.

Figure 6. Castleman's disease of the plasma cell form.

sis 1 (NF-1) but not on its own.¹⁴ Our patient did not have NF-1. Parathyroid function has not been measured routinely in these patients. In Mayo series, 14 of the 51 who were tested had low calcium, 2 had high calcium, 12 patients out of 33 had high phosphorus. This data suggests that parathyroid dysfunction should be assessed in these patients.¹⁵ Pituitary involvement in patients with POEMS syndrome is rare. Patients with a non-functioning pituitary adenoma resulting in panhypopituitarism and acromegaly have been reported.^{16,17}

Conclusions

Endocrinopathy is prevalent in POEMS syndrome. Diagnosis requires high index of suspicion and thorough investigations. These patients need long term monitoring. Management of POEMS syndrome should be multidisciplinary with involvement of endocrinologist, haematologist and neurologist.

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