A case of POEMS syndrome associated with essential thrombocythaemia and dermal mastocytosis

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Summary: We describe a case of POEMS syndrome presenting with the recognized features of polyneuropathy, organomegaly, endocrine abnormalities, monoclonal protein, skin changes and anasarca. The patient was found to have both a solitary sclerotic plasmacytoma of the pelvis and evidence of Castleman's disease of lymph nodes. A number of unusual and unique features are also documented. Histological examination of affected skin demonstrated changes similar to urticaria pigmentosa including local oedema and mast cell infiltration. There was marked thrombocythaemia which has been seen in only one previous case and in addition the patient developed diffuse vascular calcification in the absence of recognized aetiological factors. Radiotherapy of the pelvic lesion and chemotherapy to control the myeloproliferative disorder gave rise to significant improvement in neuropathy. Control of anasarca required steroid therapy in addition to diuretics. The significance of these observations is discussed in relation to previous reports.

Introduction

The acronym POEMS syndrome\(^1\) describes a complex multi-system disorder whose major features include polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal serum proteins (M) and skin changes (S). Typical cases were described as early as 1938 by Scheinker\(^2\) and later by Crow\(^3\) and Fukase.\(^4\) In 1977 Takatsuki et al.\(^5\) were able to compile a series of 32 cases from Japan and this series has recently been increased to include 102 reported Japanese cases.\(^6\) Outside Japan the syndrome appears to be much less common, but non-Japanese cases are increasingly reported.\(^7\)

Confusion has arisen over the nomenclature of the syndrome, which has also been referred to as the P E P syndrome,\(^8\) Takatsuki’s syndrome,\(^9\) and more commonly the Crow-Fukase syndrome.\(^6\) Further confusion has arisen because of the variability of the clinical presentation. To date there is no single feature of POEMS which has been attributed to every reported case and many otherwise typical cases have presented with unique associated features.

We have recently encountered a patient who presented with essential thrombocythaemia and progressed to fulfil all the classical criteria of POEMS syndrome in addition to several other unusual features, mast cell infiltration of the dermis, premature arterial calcification and cold agglutination.

Case report

A 38 year old Caucasian woman first presented in April 1985. Over the previous 6 months she had experienced weight loss in excess of 10 kg and more recently had noticed ankle oedema and uncomfortable abdominal distention.

Physical examination on presentation revealed massive hepatomegaly (10 cm), with ascites and dependent oedema. In addition there was significant lymphadenopathy in the left axillary and inguinal regions. Initial investigations revealed a raised haemoglobin 18.5 g/dl, a white cell count of \(12 \times 10^9/\text{l}\) with a normal differential count and an elevated platelet count of \(650 \times 10^9/\text{l}\). Abdominal ultrasound examination confirmed hepatomegaly, with gross ascites and also demonstrated splenomegaly. Serum biochemistry, including liver function tests was normal. Skeletal survey demonstrated a 10 cm osteosclerotic lesion in the pelvis overlying the left acetabulum (Figure 1). Axillary and inguinal lymph node biopsies showed non-specific hyperplasia.

Exploratory laparotomy demonstrated smooth hepatomegaly and splenomegaly, with no significant abdominal or retroperitoneal lymphadenopathy. Splenectomy and open liver biopsy were performed and 6 litres of ascitic fluid were drained.
Ascites quickly re-accumulated and pleural effusions and peripheral oedema worsened.

The patient was transferred to our care in October 1985, by which time she had developed amenorrhoea and profound loss of power in the lower limbs, associated with paraesthesia. She was noted to have a pigmented rash of her arms and legs with thickened hyperkeratotic areas, excessive local hair growth over the legs and abdomen and facial telangiectasia. Examination confirmed previous findings and, additionally, demonstrated marked weakness of the lower limbs, most profound in distal muscle groups (Grade 1). Muscle tone in the lower limbs was decreased and tendon reflexes and plantar responses were absent. Vibration, thermal and propioceptive sensations were normal, but light touch and pin pric sensation were hyperaesthetic. Neurological examination of the cranial nerves and upper limbs was normal. Fundoscopy demonstrated bilateral papilloedema.

Blood counts on presentation demonstrated polycythaemia and thrombocythaemia, as detailed above. By October 1985, her haemoglobin was 14.9 g/dl, RBC 6.37 \times 10^{12}/l, MCV 79 fl, MCH 23.7 pg, with a white blood cell count of 18.5 \times 10^{9}/l. Differential white cell count was, neutrophils 13.3 \times 10^{9}/l, lymphocytes 3.3 \times 10^{9}/l, monocytes 1.67 \times 10^{9}/l. The platelet count remained elevated at 1440 \times 10^{9}/l and serial counts rose above 2000 \times 10^{9}/l. The blood film showed post splenectomy changes in addition to hypochromasia and microcytosis. Serum ferritin <10 \mu g/l, (normal 12–250 \mu g/l) confirmed marked iron deficiency, serum folate 3.9 \mu g/l, (normal 2–10 \mu g/l) and red cell folate 75 \mu g/l, (normal 130–800 \mu g/l) and serum B12 125 ng/l, (normal 150–1000 mg/l) were low. Bone marrow aspirate demonstrated grossly increased cellularity, affecting all elements, but predominantly the megakaryocyte series. Plasma cells were slightly increased but accounted for less than 5% of marrow elements and marrow iron reserves were depleted. The ESR was initially normal (8 mm/h), but rose after the first 3 months of treatment to over 100 mm/h, due to the development of anti-I cold agglutinins, with a titre of 1:1048, (normal < 1:64) which persisted for several months before returning to normal.

Serum biochemistry and liver function tests were within normal limits. Creatinine clearance was decreased (67 ml/min), serum urea 10.7 mmol/l, (normal 2.5–7.5 mmol/l) and serum creatinine 130 \mu mol/l, (normal 10–120 \mu mol/l) were mildly elevated. Serum and urinary porphyrins were not elevated. Serum immunoglobulin concentrations were normal. Immuno-electrophoresis demonstrated an IgG(\lambda) monoclonal serum protein, Bence Jones proteinuria was absent and urinary light chain estimations were normal. Urinary histamine estimations performed after initial chemotherapy were within normal limits.

All endocrine investigations were conducted at least 2 months after the development of amenorrhoea. Serum prolactin was persistently elevated with levels of 1000 to 1840 IU/l (normal < 600 IU/l) in the absence of any pharmacological stimulus to secretion. FSH and LH levels were undetectable on three separate occasions, whilst serum oestradiol was elevated 68–104 pmol/l, (normal < 37 pmol/l). Thyroid function tests were consistently abnormal, with low levels of thyroid hormones triiodothyronine (T3) 0.6–0.8 nmol/l, (normal 1.1–2.8 nmol/l), thyroxine (T4) 46–74 nmol/l, (normal 15–150 nmol/l) and moderately raised thyroid stimulating hormone (TSH) levels 7–9 mU/l, (normal < 5 mU/l). The patient remained clinically euthyroid throughout treatment. Serum cortisol and growth hormone levels were normal and showed normal diurnal variation.

Antibodies to gastric parietal cells were detected at a titre of 1:256. Rheumatoid factor, antinuclear antigen, and antibodies to extractable nuclear antigen, ribonuclear protein, smooth muscle, striated muscle, mitochondria, thyroglobulin, thyroid microsomes and acetylcholine receptors were all absent. Serum complement assays were normal on three separate occasions and immune complexes were not detected.

Cerebrospinal fluid (CSF) protein was elevated 1.24 g/l, (normal 0.25–0.75 g/l) and the CSF pressure was raised at 29 cm of water. Cytospin examination of the CSF revealed occasional lymphocytes, but no abnormal cell types. Electromyography confirmed absent sensory and motor
responses in the legs and reduction of the maximal velocity of propulsion of sensory and motor potentials in the upper limbs. Motor responses were small, with broadened complexes, but were not polyphasic. These findings demonstrated a sensorimotor polyneuropathy with lower limb and motor emphasis.

Chest radiography at presentation demonstrated a small right sided pleural effusion and basal atelectasis, but was otherwise normal. Repeat skeletal radiographs in March 1986 showed extensive vascular calcification in the small vessels of the pelvis, legs and arms. A $^{99m}$Tc pertechnetate bone scan demonstrated an increase in uptake related to the acetabular lesion with no other apparent abnormality. A CT scan of the brain was normal.

Review of the original lymph node biopsy demonstrated marked follicular hyperplasia, with vascular endothelial proliferation and numerous plasma cells in the interfollicular spaces. Liver biopsy was normal. The spleen weighed 629 g and histological examination demonstrated congestive splenomegaly, with follicular hyperplasia and widespread hyaline debris. Cytology of ascitic fluid showed inflammatory cells with polymorphs, lymphocytes, mesothelial cells and numerous histocytes but no malignant cells.

Skin biopsy (Figure 2), using liquid nitrogen freezing showed a hyperkeratotic but otherwise unremarkable epidermis. The dermal collagen fibres were widely separated by oedema fluid. The dermis contained large numbers of mast cells and in addition there was perivascular, predominantly lymphoid, inflammatory cell infiltrate. No deposition of immunoglobulins or evidence of complement activation was demonstrated.

Biopsy of the osteosclerotic pelvic lesion demonstrated numerous plasma cells throughout the bony interstitium.

Treatment and progress

A diagnosis of POEMS syndrome was made. Initial treatment was directed at control of myeloproliferative activity and anasarca with cytosine arabinoside and thioguanine followed by maintenance with thioguanine which gave adequate control of platelet levels. She was simultaneously treated with radioactive phosphorus ($^{32}$P, 200 MBq). Long term anticoagulant therapy with nicoumalone was also initiated.

The major clinical problem at this point was anasarca and initial diuretic treatment was entirely unsuccessful until the addition of prednisolone (60 mg/day), which resulted in significant weight loss and clinical improvement. The patient remained on a small maintenance dose of steroids and was well for 6 months until she relapsed with gross anasarca and bilateral pleural effusions following an apparent viral infection. Diuretics combined with increased prednisolone dosage resulted in weight loss from 95 to 75 kg, but oedema recurred on reducing the steroid dose to 7.5 mg/day and did not respond to an intensification of diuretic treatment. By December 1986 she again required para-centesis, which was complicated by Staphylococcus...
raised CSF paralysis has in as motor with drome most typical absence of case.14 polyneuropathy type generalized polyclonal dyscrasia.6'13 Present I) Polyneuropathy Peripheral neuropathy 100 + Papilloedema 65 + Raised CSF protein 96 + Organomegaly Hepatomegaly 76 + Splenomegaly 26 + Lymphadenopathy 60 + Endocrinopathy Gynaecomastia (male) 72 NA Impotence (male) 69 NA Amenorrhoea (female) 100 + Impaired glucose tolerance 49 + Hypothyroid 9 + Addisonian 3 – M-Band Solitary bone myeloma 58 + Increased marrow plasma cells 38 + Monoclonal protein 59 + Skin lesions Hyperpigmentation 92 + Thickening 85 + Hirsutes 72 + Hyperhidrosis 62 + Oedema Peripheral oedema 90 + Ascites 39 + Pleural effusion 68 + Haematological Polycythaemia 17 + Leukocytosis 31 + Thrombocytosis 4 + Raised ESR 71 + Other features Fever 46 – Clubbing 54 – Raynaud’s phenomenon 8 –

Figures for frequency represent the percentage occurrence calculated from a review of 158 previously reported cases.

A relationship between multiple myeloma, solitary myeloma of bone and peripheral neuropathy was recognized many years before the description of POEMS syndrome.17–21 Some of these patients have an IgM gammopathy with specific antibody activity against myelin-associated glycoprotein (MAG), others develop polyneuropathy secondary to amyloid infiltration.22–24 Other early reports of neuropathy associated with myeloma clearly represent cases of POEMS syndrome.9,17,19 Although the k/λ ratio in lytic multiple myeloma and solitary myeloma of bone is 2:1, 73% of patients with POEMS syndrome and 83% of patients with multiple myeloma and polyneuropathy show λ light chain production.5,19 Further-
more many of those patients with myeloma and k-light chain production consist of patients with anti-MAG antibody or amyloid deposition. It therefore seems that k light chain production is a feature of the great majority of patients with both POEMS syndrome and solitary myeloma associated with Guillain-Barre type neuropathy.

There are several striking similarities between the cutaneous changes in systemic mastocytosis, urticaria pigmentosa and those in cases of POEMS syndrome. Patients with urticaria pigmentosa also show marked skin thickening and mild hyperpigmentation, skin histology demonstrates numerous mast cells with some epidermal oedema. There are, however, several striking differences and the distressing itch and urtication, which are cardinal features of urticaria pigmentosa are not described in POEMS syndrome.

The present case presented with evidence of a myelo-proliferative disorder, with a striking thrombocythaemia accentuated by splenectomy. Polycythaemia and leukocytosis are recognized associations of both POEMS syndrome and of myeloma associated with peripheral neuropathy. Thrombocythaemia has also been described in isolated cases but markedly raised platelet counts and striking bone marrow hyperplasia have been described in only one previous case.

Endocrine abnormalities are another, major, typical feature of POEMS syndrome, commonly presenting with amenorrhoea in the female and impotence in the male. Endocrine investigations typically show decreased gonadotrophins, TSH, T4 and T3 with increased oestriol, suggesting a mild under-activity of the level of the hypophysis. These findings have been discussed at length by other workers.

POEMS syndrome is also associated with evidence of both macro- and microangiopathic abnormalities. A number of workers have described patients with POEMS syndrome developing severe obliterative vascular disease of the lower limbs. Histologically these patients showed atheromatous changes and in one case monoclonal IgA immunoglobulin was detected within the thickened vessel walls. Trentham et al. felt that the disease was largely a manifestation of microangiopathic vascular damage due to a primary connective tissue disease. Despite the frequency of large vessel disease, generalized vascular calcification of the type seen in the present case seems to be rare. Capillary proliferation is a common feature in the skin, where telangiectasia, capillary haemangioma, cherry-type haemangioma and haemangioendotheliomas have been described.

Abnormalities of capillary permeability have been suggested to explain the common features of subcutaneous oedema and anaemia. The mechanism of increased permeability is unknown; however mast cells are known to proliferate in areas of neovascularisation and produce factors which increase capillary permeability.

The findings of Castleden's disease of lymph nodes (giant lymph node hyperplasia) is also increasingly associated with POEMS syndrome. Castleden et al. described a form of angiofollicular hyperplasia of mediastinal lymph nodes, histologically characterized by follicular hyper trophy due to spindle cell proliferation and associated with multiple arborizing thick walled capillaries. A second form of Castleden's disease is now recognized with sheets of mature plasma cells in interfollicular tissue in addition to the other typical features described above. This plasma cell type often occurs in non-mediastinal lymph nodes and is similar to the findings in the lymph node biopsies in the present case. Lymphadenopathy is a well recognized association of POEMS syndrome and typical Castleden's disease histology has now been described in many cases, both in association with other plasma cell dyscrasias and with mono or polyclonal gammopathy. Typical POEMS syndrome has been described in association with an apparent single abdominal focus of Castleden's disease and in a case of giant lymph node hyperplasia.

Most cases of POEMS syndrome show significant if temporary responses to treatment of the underlying plasma cell abnormality. Surgical excision or local radiotherapy of localized lesions and alkylating agents with or without steroids for disseminated plasma cell dyscrasias have all resulted in improvement of neuropathy, ana sarca and skin changes. Several workers have found that, as in the present case, diuretic therapy is ineffective in controlling fluid retention without the addition of steroids and that relapse occurs on steroid withdrawal. Death in POEMS syndrome generally results from the complications of neuropathy and ana sarca rather than from myeloma. Many patients improve or stabilize with therapy for periods of many years.

The most frequent finding of plasma cell dyscrasia has led many to implicate plasma cells in the genesis of all or many features. The relationship between peripheral polyneuropathy and monoclonal production of light chains led to the proposal of anti-neural activity by the Lambda chain. This has not been substantiated but other workers have suggested that non-immunoglobulin biologically active factors are produced by plasma cells. It is unlikely that POEMS syndrome has an autoimmune basis although overlap between features of systemic sclerosis and other connective tissue disorders have been described. Only anti-hyphosyphilis autoantibodies have been repeatedly demonstrated in POEMS syndrome, and...
the common finding of hypothryseal underactivity has led some authors to suggest that autoimmune hypothryseal hypofunction is responsible for many features of POEMS syndrome.

The suggestion that one or more unrecognized angiogenic or vasoactive factors are involved in the expression of POEMS syndrome seems likely.29-30 Recently, plasma cells in multiple myeloma have been shown to produce interleukin 6, which acts as an autocrine growth regulator and also stimulates haemopoietic stem cells.51 Indeed both interleukins 3 and 6 produce bone marrow hyperplasia and stimulation of macrophages and mast cells which in turn produce angiogenic factors and microvascular abnormalities.52 Further evidence to support the hypothesis that such factors are involved in POEMS syndrome may come from bone marrow culture studies and measurements of peptide regulatory factors.

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