Sclerodermatous lesions in a male diabetic presenting with primary infertility and neuropathy

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A 44 year-old man being followed regularly by an endocrinologist for diabetes mellitus for the past 10 years, and having polyneuropathy for the last 2 years was referred to dermatology clinic for asymptomatic skin lesions on the abdomen. The patient gave a history of primary infertility for 13 years, his semen examination showed azoospermia. About 8 years ago, the patient did TESE (testicular sperm extraction) under spinal anesthesia, but it revealed negative result for sperm retrieval. Abdominal examination showed mild hepatosplenomegaly without ascites and pretibial edema. Lymph nodes were not palpable. Scrotal examination revealed bilateral small, soft testes.

Cutaneous examination showed unilateral, asymptomatic, erythematous to brownish, none pitting edematous, indurated plaques on left side of abdomen (Fig. 1 A,B)

Differential diagnosis kept for the skin lesion included scleredema and morphea. Punch biopsy was taken from the plaque and the histopathological examination showed excessive deposition of mucin in dermis separating swollen collagen bundles +ve for alcian blue. It was consistent with scleredema (Fig. 2,3)

Radiographic skeletal survey showed no abnormal findings. Thoraco-abdomino-pelvic computerized tomography showed mild hepatoslenomegaly and small sized testes. Electromyography (EMG) was consistent with a demyelinating polyneuoropathy.

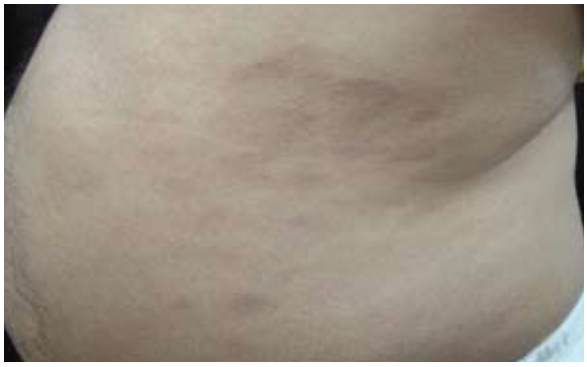

Fig. 1A. Reddish-brown plaques on left side of abdomen.

Fig. 1B. Close up of the lesions showing oedematous appearance of the plaque.

Ophthalmic examination by ophthalmologists revealed no papilledema.

Laboratory investigation revealed thrombocytosis (platelet count: 750,000/mm^3) and hyperglycemia (blood sugar: 320mg/dl). Biochemical markers for liver, kidney, thyroid gland, parathyroid gland and adrenal gland were normal. ASOT was normal. Serum vitamin B_{12} level was low at 140.0Pg/ml (normal range: 174.0-878.0). Hormonal assay for gonads and pituitary showed hypogonadotrophic hypogonadism with FSH 2.05muI/ml (3.4-21.6),

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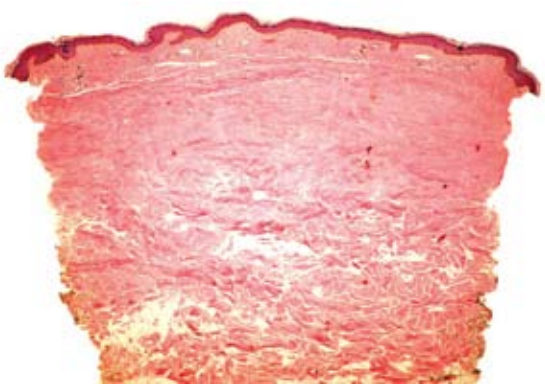

Fig. 2 Histopatholgy(H & E).

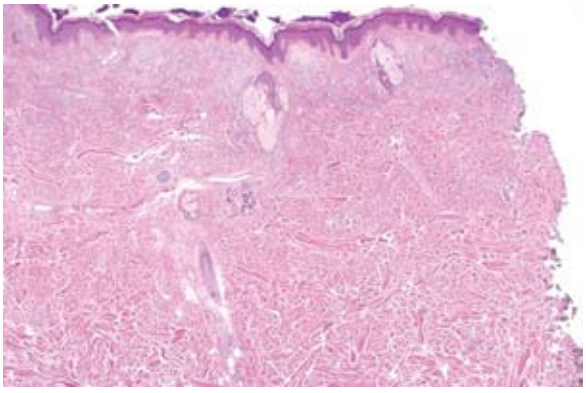

Fig. 3 Alcian Blue staining.

LH 0.22muI/ml (2.4-6.6), estradiol 13.0pg/ml (21-251), serum prolactin was normal. Serum immunofixation revealed monoclonal gammopathy of IgG lambda type (2.120g/dl). The bone marrow biopsy showed no abnormal findings.

The patient was treated with prednisolone 20mg /day, there was marked improvement in skin lesions with residual pigmentation occurring within one month, platelet count returned to the normal level but IgG gammopathy was at the same level. At the same time the patient was followed with endocrinologist for polyneuropathy, DM, hepatosplenomegaly.

What is the clinical diagnosis?

1. Urticarial vasculitis
2. Scleredema
3. POEMS syndrome
4. Hyper IgE syndrome

The diagnosis is POEMS syndrome.

DISCUSSION

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare, multisystemic disease that is associated with an underlying plasma-cell-dyscrasia. Some of the other synonymous terms used are: Osteosclerotic myeloma, Crow-Fukase syndrome and Takatsuki syndrome. Diagnosis requires two major criteria and at least one minor criterion. Major criteria include monoclonal gammopathy (almost always lambda) and polyneuropathy and the minor criteria include sclerotic bone lesions, Castleman disease, papilledema, peripheral edema, ascites, effusions, thrombocytosis, polycythemia and skin changes (pigmentation, heamangioma, hypertrichosis, sclerodermoid lesion).[1,2,3]

In our patient, polyneuropathy and monoclonal IgG gammopathy were present as a major criteria. Among minor criteria, the patient had skin lesion (scleredema), DM and hypogonadism as endocrinopathy, hepto-splenomegaly as organomegaly and thrombocytosis. Our patient met the criteria for POEM syndrome.

The pathophysiology by which plasma cells lead to POEMS syndrome is poorly understood, but elevations in VEGF, interleukin-6, tumor necrosis factor-alpha, and interleukin-1 beta have been implicated. Serum levels of VEGF are markedly elevated in POEMS syndrome patients and correlate with disease activity.[4] Because VEGF increases vascular permeability and angiogenesis, it is proposed that this may account for the organomegaly, edema, and skin hemangiomas.[4] Several

hundred cases of POEMS syndrome have been reported, but the incidence may be under reported because the syndrome can go unrecognized. Peak incidence occurs during the fifth to sixth decades of life. Peripheral neuropathy is the major clinical finding.[2] Common skin manifestations include edema of the lower extremities with diffuse hyperpigmentation, hypertrichosis, and thick skin, with tightening and sclerodermoid changes. Angiomas, in particular glomeruloid hemangiomas are characteristic. Whitening of the proximal nail, clubbing, hyperhidrosis, and Raynaud phenomenon also may be associated. The plasma-cell dyscrasias most commonly observed in POEMS patients are osteosclerotic myeloma or a monoclonal gammopathy of unknown relevance.[1,2]

Classic multiple myeloma has never been reported in association with POEMS. Immunoglobulin G-lambda chains are the proteins most frequently found.[2] Endocrinopathy is a central feature of POEMS, with hypogonadism as the most common endocrine abnormality.[3] Hypothyroidism, diabetes mellitus, adrenal insufficiency, hyperprolactinemia, and hypoparathyroidism also are observed. Many patients have more than one abnormality.[5]

Prognosis varies, but typically the course is chronic; in one study the median survival was 13.8 years. The number of POEMS features does not affect prognosis although respiratory symptoms are predictive of an adverse outcome. Within two years of diagnosis, approximately one-quarter of patients develop respiratory symptoms, which include restrictive lung disease and pulmonary hypertension. Acute ischemic strokes and myocardial infarcts have been occasionally reported in association with POEMS.[1]

Treatment of the underlying plasma-cell disorder is the major therapeutic approach. No randomized controlled trials have been performed on POEMS patients, and the information on therapy is primarily retrospective. Mainstay of treatment include radiation therapy of the osteosclerotic lesions, glucocorticoids, and alkylating agents. High-dose chemotherapy followed by stem-cell transplantation has been successful in some patients.[1,2,3]

Bevacizumab, which is a monoclonal antibody directed against VEGF, has had variable results; some patients have developed improvement in neuropathy, edema, and respiratory symptoms. While others have developed capillary leak syndrome.[6]

A multidisciplinary approach is important due to the extent of systems that may be involved in these patients. Future studies need to further examine the role of cytokines in the pathogenesis of this poorly understood disease.[7]

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