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POEMS SYNDROME – THE RARE ENDOCRINOPATHY

Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant plasma cell disorder that is characterized by the presence of serum M-protein less than 30 g/L or 3 g/dL, bone marrow (BM) clonal plasma cells less than 10%, absence of plasma cell myeloma (PCM) related end-organ damage (CRAB symptoms: hypercalcemia, renal insufficiency, anemia and, bone lesions) and absence of B-cell lymphoma or other disease known to produce an M-protein. MGUS is generally considered a preneoplastic disorder that does not always progress to overt malignancy (1, 2). Diverse endocrinopathies occur in patients with plasma cell disorders (3–6). One possible scenario is the rather rare POEMS syndrome, which is a paraneoplastic syndrome with key manifestations of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (7). We present a case study which emphasizes the importance of multidisciplinary evaluation of MGUS.

Key words: Monoclonal gammopathy of undetermined significance, Endocrinopathy, Hypogonadism, Insulin resistance

CASE STUDY

Male patient, 69 years old, was referred to University Clinic of endocrinology, Clinical center of Serbia by a neurologist, diagnosed with demyelinating polyneuropathy, complaining of 12 months long episode of tiredness, erectile dysfunction, decreased libido. Personal history: Hypertension, polydiscopathy of the cervical and lumbosacral spine, polyneuropathy. Physical examination: Hight 183 cm, Weight 78 kg, BMI 23.3 kg/ m. Findings on the heart and lungs and abdomen were normal. There was no peripheral edema, gynecomastia, but reduced male pattern virilization and distinct fingernail clubbing with whiter nails. Local genital examination: slightly reduced male-type genital hairiness, left testicle is smaller in size (orchidometer: vol 6 ml), positioned higher in the scrotal sac and softer in consistency, right testis is of

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normal volume (orchidometer vol 20 ml), consistency and position, without palpable tumors on both sides.

The biochemical analysis were in the reference range, in complete blood count erythrocytosis. Thyroid-stimulating hormone: 1,560 m IU/L; Thyroxine, free: 12.1 pmol/l ; antitpo at 10.7 IU/ml., antitg at 187.6 IU/ml ; Follicle-stimulating hormone (FSH) 8.5 IU/l, Luteotropic hormone (LH) 3.8 IU/l, Testosterone (T) total 8.52 nmol/l, Free T 177 pmol/l, Sex hormone binding globulin (SHBG) 27.8 nmol/l, Dehydroepiandrosterone (DHEAS) 4.5 umol/l, vitamin D 54 nmol/l, Parathyroid hormone (PTH) 57ng/l. Cortisol 471 nmol/l, Adrenocorticotropic hormone (ACTH) 36.5, PRL 236 mIU/l, OGTT: glucose 6.4… 9.0… 11.2… 10.7… 6.3 mmol/l, Insulin 93.13… 691.86… 1236.21… 1403.58… 493.10 pmol/l. HOMA IR 3.8. ECHO of the thyroid gland: The thyroid gland is of regular position and size, coarser homogeneous echostructure, usual CD signal, without any structural malformations. ECHO of the scrotum showed normal right (vol 20 ml) and heterogenous small left testicle (vol 6 ml), with dilated veins of the pampiniform plexus up to 2 mm. Chest radiography and abdominal ultrasonography was normal. Dual X ray absorptiometry (DXA) showed sclerotic bone lesions. At the same time the patient underwent hematologic investigations. Serum protein electrophoresis: Weak suspect of paraprotein; Monoclonal Ig kappa type was identified by immunofixation of serum proteins.

A diagnosis of (central) hypogonadism, chronic thyroiditis with preserved thyroid function, hypovitaminosis D and insulin resistance was made, along with Light-chain MGUS. The patient was prescribed with Testosterone depot 250 mg i.m. on 21 days, cholecalciferol 2000 IU/day and Metformin 500 mg per day. Follow-up is planned in a month and the close follow up was indicated by a hematologist.

DISCUSSION

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant plasma cell disorder that is characterized by the presence of serum M-protein less than 30 g/L or 3 g/dL, bone marrow (BM) clonal plasma cells less than 10%, absence of plasma cell myeloma (PCM) related end-organ damage (CRAB symptoms: hypercalcemia, renal insufficiency, anemia and, bone lesions) and absence of B-cell lymphoma or other disease known to produce an M-protein. MGUS is generally considered a preneoplastic disorder that does not always progress to overt malignancy (1, 2). There are three distinct types of MGUS (8):

1. Non-IgM MGUS: Non-IgM MGUS (IgG, IgA, Ig D) accounts for the majority of MGUS cases and is characterized by a monoclonal plasma cell.
2. IgM MGUS
3. Light-chain MGUS

Light chain MGUS (LC-MGUS), as in presented patient, is characterized by a monoclonal protein that lacks the immunoglobulin heavy chain component, it may show progression to idiopathic Bence Jones proteinuria, light chain PCM, AL amyloidosis, or light chain deposition disease. The risk of progression to multiple myeloma in patients with light-chain MGUS is 0.3% (9, 10)

MGUS is found in approximately 2% to 3% of adults over age 50 and in 5% of adults older than the age of 70. MGUS is more common in men than in women (1, 5:1). Population based studies show increased risk of MGUS among first-degree relatives of those with MGUS or myeloma, supporting a role for germline susceptibility genes, shared environmental influences, or an interaction between both (11, 12). Diverse endocrinopathies occur in patients with plasma cell disorders (3–6). Sometimes, instead of the signs typically observed in MG, the most revealing symptoms are those of a dysfunctional endocrine system, thus confounding the diagnosis of MG. One such disease scenario is the rather rare POEMS syndrome, coined by Bardwick in 1980, which is a paraneoplastic syndrome with key manifestations of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (7), with only a limited number of retrospective series reported so far (13, 14). Distinctive characteristics of the syndrome that differentiate POEMS syndrome from standard multiple myeloma (MM) include the following: (1) dominant symptoms are typically neuropathy, endocrine dysfunction, volume overload; (2) dominant symptoms have little to nothing to do with bone marrow infiltration by plasma cells, or renal failure; (3) vascular endothelial growth factor (VEGF) levels are high; (4) sclerotic bone lesions are present in the majority of cases; (5) overall survival is typically superior; and (6) lambda clones predominate (15).

Recent data indicate that endocrine dysfunction in patients with MG may be related to the production of growth factors as well as of cytokines such as IGFBP-2 and IGFBP-3, VEGF, IL-1β, IL-6, and TNF-α by tumor cells or their microenvironment (16–20). Being transportable via the blood circulation, these molecules not only exert local proangiogenic and proliferation effects on the tumor cells themselves and their immediate environments (21, 22) but also influence cellular metabolism at systemic level through autocrine, paracrine, and endocrine pathways (23, 24).

To date, VEGF is the cytokine that correlates best with disease activity, although it may not be the driving force of the disease based on the mixed results seen with anti-VEGF therapy (25–28). Also, VEGF is known to target endothelial cells, induce a rapid and reversible increase in vascular permeability, and be important in angiogenesis. It is expressed by osteoblasts, macrophages, tumor cells (including plasma cells) and megakaryocytes/platelets (29–30). A remarkable observation was that both polyclonal plasma cells and clonal plasma

cells had equally high levels of intracellular VEGF though monoclonal PCs had higher levels of intracellular IL-6 expression. Both IL-1β and IL-6 have been shown to stimulate VEGF production (31). Plus, IL-12 has also been shown to correlate with disease activity which highly accentuates proinflammatory cytokine profile (32).

The 2021 criteria for diagnosis of POEMS were published aiming for prompt recognition of the rare paraneoplastic syndrome (15). Mandatory major criteria: 1. Polyneuropathy (typically demyelinating), 2. Monoclonal plasma cell-proliferative disorder (almost always λ). Other major criteria (one required): 1. Castleman disease, 2. Sclerotic bone lesions, 3. Vascular endothelial growth factor elevation. Minor criteria: 1. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy), 2. Extravascular volume overload (edema, pleural effusion, or ascites), 3. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic), 4. Skin changes (hyperpigmentation, hypertrichosis, hemangiomas, plethora, acrocyanosis, flushing, white nails), 5. Papilledema, 6. Thrombocytosis / polycythemia. Other symptoms and signs: weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values.

Our patient was eligible for mandatory major criteria, one major criteria (we could not perform VEGF measurement) and three of the minor criteria (endocrinopathy, polycythemia, skin changes) which led to diagnosis of POEMS syndrome.

Endocrine dysfunction in POEMS syndrome patients can be both central and peripheral (33, 34). The most frequent presentations are related to hypogonadism, thyroid dysfunction, and impaired glucose metabolism, as in was shown in presented patient. Adrenal insufficiency has also been described in both the American and Japanese patients (35). To date, it is believed that these abnormalities are not the consequences of structural damages to the endocrinal tissues (36); The present evidence does not support the hypothesis of autoimmunity against endocrine tissues (33). From a broader point of view, for patients presenting with endocrine dysfunction associated with plasma cell disorder, targeting cytokine signaling may represent an additional therapeutic tool. In rodents and primates with hypogonadism, the hyperreactivity of the HPA axis due to stress and increased cytokines such as IL-6 was attenuated by sex hormone replacement (37–39). In postmenopausal women, estradiol replacement alleviated endotoxin-stimulated release of ACTH, cortisol, and cytokines (38). The correction of endocrine dysfunction could thus be beneficial for the amelioration of cytokine profile. Further studies are necessary to determine the clinical relevance of these experimental data. The case has alerted us to be aware of the possible association of endocrine disfunction with monoclonal gammopathy.

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