NOTE

Abnormal FSH Hypersecretion as an Endocrinological Manifestation of POEMS Syndrome

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Abstract. Two patients with POEMS syndrome had high basal levels of FSH in the absence of primary hypogonadism. They were fertile eugonadal men with normal serum testosterone and estradiol levels. Provocation with LH-releasing hormone revealed blunted response of FSH secretion, but normal response of LH secretion in both patients, and one had pituitary microadenoma on brain MRI. This report adds primary FSH hypersecretion in the absence of primary testicular failure to the list of endocrinopathy of POEMS syndrome.

Key words: POEMS syndrome, Gonadotropin, Pituitary microadenoma

POEMS syndrome, a multisystem affliction of poor prognosis, takes its acronym name from its most frequent signs: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin lesions. The syndrome, also known as Crow-Fukase or Takatsuki syndrome, has most frequently been reported in Japan [1], but exists in non-Asian populations as well [2, 3], and is often associated with osteosclerotic myeloma or solitary plasmacytoma, and with other clinical and pathologic signs such as fever, sweating, peripheral edema, thrombocytosis and finger clubbing.

The endocrinopathy is complex and often combined with more than one of the following: diabetes, hypothyroidism, hypogonadism with amenorrhea and impotence, gynecomastia, hyperprolactinemia and hyperestrogenemia [1, 3–7]. Hormonal abnormality described in the literature, such as hypothyroidism, is either primary or secondary [3], and it is difficult to ascribe such diverse involvement to a single pathogenetic factor. Hypersecretion of gonadotropins observed in POEMS syndrome has only been described as a result of primary gonadal failure [7]. Here we report two patients associated with abnormal FSH hypersecretion in the absence of primary hypogonadism, one with a pituitary tumor, thus adding to the spectrum of endocrine changes associated with POEMS syndrome.

Case Reports

Case 1

A 63-year-old man was well until March, 1992, when he first noted chest oppression, dyspnea, palpitation and easy fatigability. In May, 1993, he was admitted and diagnosed as having hypertrophic cardiomyopathy, excessive perspiration, more than ten cutaneous angiomas, and a painful sensorimotor peripheral neuropathy, and laboratory examination revealed monoclonal protein (IgG λ). He was diagnosed as having incomplete form of POEMS syndrome because of a lack of endocrinopathy. In
1994, numbness of his lower extremities and lumbago developed and progressed thereafter, and was not alleviated by anesthesiologic management. He was readmitted on October 2, 1996, because of intractable backache. Magnetic resonance imaging (MRI) and roentgenography of the lumbar spine did not reveal any evidence of lumbar myelopathy. The M component of IgG λ persisted, but bone marrow aspiration test was unremarkable. He did not present any signs or symptoms suggestive of hypogonadism with a normal testicular size (16.5 ml); he had one child. Endocrine examination revealed a noticeable marked increase in serum gonadotropin levels: FSH, 55.2 IU/L and LH, 43.4 IU/L. The following serum hormone levels were normal: testosterone, 8.3 nmol/L; estradiol, less than 36.7 pmol/L; free thyroxine, 14.2 pmol/L; free triiodothyronine, 4.6 pmol/L; TSH, 0.5 mU/L; GH, 0.49 µg/L; ACTH, 2.86 pmol/L; PRL, 2.2 µg/L; cortisol, 168 nmol/L and somatomedin C, 0.60 U/mL. Stimulation with LH-RH (100 µg) revealed blunted FSH response, but exaggerated LH response (Fig. 1). Provocation with CRH (100 µg), GRH (100 µg), and TRH (500 µg) resulted in normal responses of ACTH, GH, TSH and PRL secretion, respectively. MRI of the brain disclosed a pituitary microadenoma (5 mm in diameter).

**Case 2**

A 65-year-old man first noted his right cervical tumor in 1982. He had been treated for non-insulin dependent diabetes mellitus with oral hypoglycemic agents and dietary restriction since then. In 1987, he started to feel numbness and pain in the feet which progressed to both upper thighs and forearms. In March, 1989, muscle weakness of the lower extremities developed, followed by painful paresthesia, which progressed and made him unable to walk in April. Biopsy of his cervical tumor revealed granulomatous lymphadenopathy with noticeable plasma cell and lymphoid cell infiltration. Serum and cerebrospinal fluid revealed the presence of IgG λ M protein. Systemic distal muscular atrophy was noted. Nerve conduction velocities and sensory evoked responses were slowed. Sural nerve biopsy showed axonal degenerative changes. These data are compatible with the diagnosis of POEMS syndrome except for the lack of skin lesions. He was treated with prednisolone and melphalan, which alleviated muscle weakness and painful sensory disturbances, and reduced his cervical mass and monoclonal protein. In November, 1995, he was readmitted
He did not present any signs or symptoms suggestive of hypogonadism with a normal testicular size (17 ml); he had five children. Endocrine examination revealed a marked increase in serum FSH (38 IU/L), but a normal serum LH concentration (9.3 IU/L). Other hormones were normal: testosterone, 19.0 nmol/L; estradiol, 83.0 pmol/L; free thyroxine, 18.1 pmol/L; free triiodothyronine, 4.6 pmol/L; TSH, 0.34 mU/L; GH, 0.33 µg/L; ACTH, 5.28 pmol/L; PRL, 5.0 µg/L and cortisol, 320 nmol/L. Stimulation with LH-RH revealed blunted FSH response, but normal LH response. CT scan and MRI of the pituitary did not show any abnormality. His diabetes was well controlled with dietary restriction and glibenclamide. In October, 1996, he was found to have squamous cell carcinoma of the right lower lobe of the lung, which was successfully resected, but he died of metastatic lung cancer in July, 1997; no autopsy was performed.

Discussion

The two patients described herein had five main features (except skin lesion in case 2), which easily confirmed the diagnosis of POEMS syndrome. Multiple endocrine organ failure, including primary gonadal failure, is common in the POEMS syndrome and yet the absence of endocrinopathy does not exclude the diagnosis. Both patients had high basal FSH, which was the sole and peculiar endocrine manifestation. Although no semen analysis was performed, both patients appeared to have no symptoms or signs suggestive of primary hypogonadism and were fertile with normal testicular size for their ages.

The basal gonadotropin levels in the elderly may vary depending upon the decreased testicular function due to aging [8-10], but the basal levels of testosterone and estradiol in both patients were within the normal range for their ages. Stimulation with LH-RH usually causes greater gonadotropin secretion [9]. In the present two patients, stimulation with LH-RH resulted in exaggerated (Case 1) and normal (Case 2) responses of LH, whereas the FSH response was blunted in both patients (Fig. 1). By contrast, secretion of other pituitary hormones was normal. The higher basal secretion of FSH and the failure of normal response of FSH to LH-RH in these patients suggested selective abnormal secretion of FSH in these patients. In fact, MRI showed Case 1 to have a pituitary microadenoma.

The mechanism for abnormal secretion of FSH in POEMS syndrome remains unknown. Cytokines, such as interleukin (IL)-6, IL-1β and tumor necrosis factor-α, have been reported to increase in POEMS syndrome and suggested to mediate systemic manifestations of POEMS syndrome [11, 12]. It has been shown that ILs stimulates secretion of FSH and LH in rats [13], although others reported complicated roles for gonadotropin secretion [14, 15]. Cytokines are generally known to cause mitogenic effects in a variety of tissues, including pituitary cells [16, 17]. Therefore it is possible to speculate that an activated cytokine network may cause proliferation of pituitary gonadotrophs, thereby leading to hypersecretion of gonadotropin. If this is the case, the cellular mechanism by which cytokines act on FSH-secretory cells more selectively than LH-producing cells remains to be determined.

It is not yet known whether the abnormal FSH hypersecretion derives from FSH-producing adenoma and/or hyperplastic gonadotrophs in our patients. It has been reported that patients with FSH-secreting adenomas have much higher basal FSH levels, which are unresponsive to LH-RH, with normal to high LH levels, and may show signs of secondary hypogonadism [18, 19]. These endocrine features of FSH-producing adenoma are consistent with those of our patients except for the absence of secondary hypogonadism. Unfortunately, Case 2 succumbed to metastatic lung cancer and pituitary exploration could not be performed. A thorough follow-up of pituitary by brain MRI and serum gonadotropin determinations in Case 1 are therefore needed to see whether an overt FSH-producing adenoma may develop to be removed by surgery.

Physicians should be well aware that a high gonadotropin concentration in POEMS syndrome is not always secondary to primary gonadal failure, but may be primarily due to abnormal hypersecretion of gonadotropins. Hypersecretion of gonadotropin due to primary hypogonadism and primary pituitary lesion should be carefully differentiated in POEMS syndrome.
References


12. Gherardi RK, Bellec L, Fromont G, Divine M, Malapert D, Gaulard P, Degos JD (1994) Elevated levels of interleukin-1β (IL-1β) and IL-6 in serum and increased production of IL-1β mRNA in lymph nodes of patients with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome. Blood 83: 2587–2593.


