INTERNAL MEDICINE

□ CASE REPORT □

Fibromyalgia in a Patient with Cushing's Disease Accompanied by Central Hypothyroidism

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Abstract

A 39-year-old woman with a 3-year history of a rounded face developed widespread myalgia. Detailed examinations revealed no disorders that could explain the pain other than concomitant Cushing's disease and central hypothyroidism. Both the hypercortisolemia and hypothyroidism completely resolved after the patient underwent surgery to treat Cushing's disease, but she continued to experience unresolved myalgia and met the diagnostic criteria for fibromyalgia. Few studies have so far investigated patients with fibromyalgia associated with Cushing's syndrome. In our case, the hypothyroidism caused by Cushing's disease probably played an important role in triggering and exacerbating fibromyalgia. This highlights the need to examine the endocrine function in patients with muscle pain.

Key words: fibromyalgia, central hypothyroidism, Cushing's disease, analgesics, transsphenoidal surgery, muscle biopsy

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Introduction

Fibromyalgia is a chronic disorder characterized by widespread muscle pain that is often accompanied by fatigue or insomnia (1, 2). Although the etiology of fibromyalgia remains unknown, endocrinological abnormalities, such as a disturbed hypothalamus-pituitary-adrenal axis and hypothyroidism, are thought to be triggering or exacerbating factors for this disorder (3-5). In addition, fibromyalgia may occur after the withdrawal of supraphysiological doses of exogenous steroids (6) or after treatment for endogenous Cushing's syndrome (7, 8). However, few studies have so far investigated patients with fibromyalgia associated with untreated Cushing's syndrome.

Endogenous Cushing's syndrome is an endocrine disease resulting from chronic exposure to excessive glucocorticoids produced in the adrenal cortex (9). It produces physical features, such as a rounded face, truncal obesity, thin skin, and proximal muscle weakness without pain.

Cushing's disease is the most common form of endogenous Cushing's syndrome and it is caused by adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas. It is not uncommon for patients with Cushing's disease to exhibit central hypothyroidism regardless of whether their disease is due to ACTH-secreting macroadenomas or microadenomas (10).

We herein report a rare case of a patient who developed fibromyalgia during the course of Cushing's disease that was accompanied by central hypothyroidism.

Case Report

A 39-year-old Japanese woman visited a local general

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Table 1. Laboratory Findings in February 2011.

Hematology		
Red blood cells	424 × 10^4/μL	(378–499)
Hemoglobin	10.9 g/dL	(10.8–14.9)
Hematocrit	37.0 %	(35.6–45.4)
White blood cells	8,520/μL	(3,040–8,540)
Neutrophils	74.9 %	(38.0–71.0)
Lymphocytes	19.3 %	(21.0–50.0)
Basophils	0.6 %	(0.2–2.0)
Eosinophils	0.7 %	(0.2–7.3)
Monocytes	4.7 %	(3.0–8.0)
Platelets	37.7 × 10^4/μL	(15.0–36.1)
Chemistry		
Total protein	7.2 g/dL	(6.6–8.0)
Albumin	3.8 g/dL	(4.1–5.0)
Aspartate aminotransferase	16 IU/L	(13–33)
Alanine aminotransferase	22 IU/L	(6–27)
Blood urea nitrogen	9 mg/dL	(8–20)
Creatinine	0.58 mg/dL	(0.5–0.8)
Sodium	144 mmol/L	(138–146)
Potassium	3.8 mmol/L	(3.6–4.9)
Chloride	107 mmol/L	(99–109)
Creatine kinase	57 IU/L	(45–163)
Aldolase	3.0 IU/L	(2.1–6.1)
C-reactive protein	0.11 mg/dL	(< 0.30)
Erythrocyte sedimentation rate	32 mm/h	(< 15)
Fasting plasma glucose	5.3 mmol/L	(3.9–6.1)
HbA1c (NGSP)	4.9 %	(4.6–6.2)
Lactic acid	1.3 mmol/L	(0.9–1.7)
Thyroid-stimulating hormone	0.37 μU/mL	(0.60–4.10)
Free triiodothyronine	1.3 pg/mL	(2.1–3.8)
Free thyroxine	0.8 ng/dL	(0.9–1.6)
Rheumatoid factor	< 5.0 IU/mL	(< 10)
Anti-nuclear antibody	< 5.0 INDEX	(< 20)
Anti-Jo-1 antibody	< 5.0 INDEX	(< 18)
Myeloperoxidase-ANCA	< 10 EU	(< 20)
Proteinase-3-ANCA	< 3.5 U/mL	(< 3.5)

ANCA: anti-neutrophil cytoplasmic antibody, NGSP: National Glycohemoglobin Standardization Program

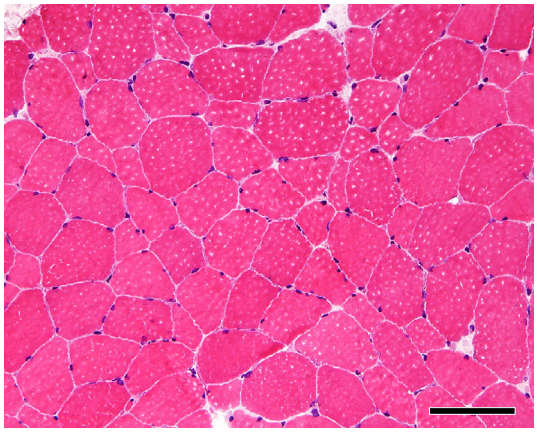

Figure 1. Microscopic findings from a biopsy specimen from the left biceps brachii muscle (February 2011). Non-specific chronic myogenic changes, including moderate fiber size variations, were observed using Hematoxylin and Eosin staining. Bar=100 μm.

hospital in February 2011 because of a 6-month history of widespread muscle pain. The patient's family history was unremarkable other than her father's sudden death; furthermore, none of her relatives had any history of muscle or mitochondrial diseases. The patient had a personal history of iron deficiency anemia and had not taken any special health foods or any medications except for oral iron supplements. She had never consumed alcohol or smoked cigarettes. She had been healthy until spring 2007 when her face became more rounded. She had moved to Niigata from the Pacific side of Japan 7 months before the visit, and the next month she developed spontaneous pain, tenderness, and exercise pain in her muscles that predominantly occurred in the extremities after the occurrence of a tingling sensation in her lower legs. Magnetic resonance imaging (MRI) revealed no apparent abnormalities in the cerebrum, cerebellum, brainstem or spinal cord. Despite the administration of oral analgesics including non-steroidal anti-inflammatory drugs, her pain worsened, and she was referred to the neurology department of our hospital for a detailed examination in February 2011.

The patient was 165 cm tall, weighed 65 kg, and her body temperature was 36.3°C. She presented with spontaneous, pressure, and exercise pain in the muscles of the neck, chest, bilateral upper and lower arms, and bilateral upper and lower legs (visual analogue scale score: 6 of 10). She experienced moderate fatigue and insomnia, waking unrefreshed, constipation, and an irregular menstrual cycle. She had mild weakness of the neck flexor muscles (manual muscle testing score: 4 of 5) and had stiffness in the hands, but no joint swelling or pain. She had no cognitive impairment, hypoacusis, quadriplegia, extrapyramidal symptoms, or ataxia. Laboratory tests showed a high-normal white blood cell count, normal serum creatine kinase, aldolase, and C-reactive protein levels, a normal blood lactic acid level, a slightly high erythrocyte sedimentation rate, and thyroid hormone level abnormalities (Table 1). Tests for rheumatoid factor, anti-nuclear antibody, anti-Jo-1 antibody, and myeloperoxidase- or proteinase-3- anti-neutrophil cytoplasmic antibody were negative. A microscopic analysis of biopsy samples obtained from the left biceps brachii muscle revealed non-specific chronic myogenic changes, such as moderate fiber size variations (Fig. 1). No necrotic or regenerated fibers, inflammatory cell infiltrate, atrophy or hypertrophy, predominance of type 1 or type 2 fibers, specific abnormal structure, ragged-red fibers, or increased expression of human leukocyte antigen class I were observed. Taken together, these test results were not consistent with those of infectious myositis, collagen disease, or autoimmune or inflammatory myopathies including polymyalgia rheumatica, and mitochondrial myopathy. Myopathy related to drug use, including statins, bisphosphonates, ciprofloxacin, and antidepressants were also ruled out due to the patient's history of no medication, except for iron supplementation for her anemia. The patient began an analgesic medication regimen that included oral gabapentin (1,800 mg/day), milnacipran hydrochloride (25 mg/day), and an extract from the cutaneous tissue of a rabbit inoculated with vaccinia virus (16 units/day) and she was referred to our department for a further endocrine evaluation in March 2011.

Table 2. Endocrinological Investigation.

A. Plasma ACTH and cortisol levels during 1 day in July 2011

	0 AM	8 AM	4 PM	12 PM
Plasma cortisol (μg/dL)	13.9	18.0	19.0	16.7
Plasma ACTH (pg/mL)	29.7	25.2	45.7	45.3

ACTH: adrenocorticotropic hormone

B. Morning plasma cortisol and ACTH levels following an overnight administration of low or high dose oral dexamethasone in July 2011

	Dexamethasone dose	
	0.5 mg	8 mg
Plasma cortisol (μg/dL)	15.3	1.8
Plasma ACTH (pg/mL)	26.6	3.7

The patient received oral dexamethasone (0.5 mg or 8 mg) at 11 PM, and blood samples were obtained the following morning at 8 AM.

C. CRH/GRF/TRH/LHRH stimulation test in July 2011

	Time (min)					
	0	15	30	60	90	120
Plasma ACTH (pg/mL)	49.8	88.2	55.3	29.7	18.7	19.5
Plasma cortisol (μg/dL)	20.5	26.0	24.8	18.7	16.5	14.5
Thyroid-stimulating hormone (μU/mL)	0.06	0.85	1.12	0.80	0.59	0.38
Growth hormone (ng/mL)	0.1	1.8	2.1	1.1	0.5	0.2
Prolactin (ng/mL)	12.5	63.7	57.9	35.0	25.4	19.4
Luteinizing hormone (mIU/mL)	2.0	8.8	13.3	18.3	17.6	18.1
Follicle-stimulating hormone (mIU/mL)	2.1	2.6	3.3	4.2	4.9	5.7

The following were intravenously administered at 8 AM: human corticotropin-releasing hormone (CRH), 100 μg; growth hormone-releasing factor (GRF), 100 μg; thyrotropin-releasing hormone (TRH), 500 μg; and gonadotropin-releasing hormone (LHRH), 100 μg. The patient underwent thyroid hormone replacement therapy with levothyroxine (75 μg/day) for her hypothyroidism and had normal serum levels of free thyroxine (1.3 ng/dL) and free triiodothyronine (2.2 pg/mL).

D. CRH/GRF/TRH/LHRH stimulation test in March 2013, 18 months after transsphenoidal surgery

	Time (min)					
	0	15	30	60	90	120
Plasma ACTH (pg/mL)	7.8	42.3	68.5	58.0	34.1	31.7
Plasma cortisol (μg/dL)	7.1	13.0	16.4	20.4	17.8	17.7
Thyroid-stimulating hormone (μU/mL)	1.33	17.00	21.53	17.33	12.28	8.60
Growth hormone (ng/mL)	0.8	2.5	2.3	1.2	1.0	0.6
Prolactin (ng/mL)	7.9	110.4	101.4	59.7	34.8	23.7
Luteinizing hormone (mIU/mL)	2.2	15.3	23.3	24.0	20.7	20.7
Follicle-stimulating hormone (mIU/mL)	2.8	3.7	4.4	5.6	5.7	6.2

The following were intravenously administered at 8 AM: CRH, 100 μg; GRF, 100 μg; TRH, 500 μg; and LHRH, 100 μg. The patient was euthyroid (free thyroxine, 1.1 ng/dL; free triiodothyronine, 3.1 pg/mL).

E. Growth hormone releasing peptide-2 stimulation test in February 2015

	Time (min)				
	0	15	30	45	60
Growth hormone (ng/mL)	0.2	6.6	13.7	11.4	7.8

Growth hormone releasing peptide-2 (100 μg) was intravenously administered at 8 AM.

At her physical examination, the patient's blood pressure and pulse rate were 123/64 mmHg and 63 beats per minute, respectively. She presented with a rounded, ruddy face, supraclavicular fat accumulation, truncal obesity, and mild pretibial edema. No thyroid struma, heart murmurs, or chest rales were detected. Her skin was thin, and she had facial acne. Laboratory findings confirmed decreased serum levels of thyroid-stimulating hormone (TSH) (0.50 μU/mL), free triiodothyronine (FT_3) (1.5 pg/mL), and free thyroxine (FT_4) (0.8 ng/dL). She tested negative for pituitary antibody, thyroid peroxidase antibody, thyroglobulin antibody, and TSH receptor antibody. Ultrasonography revealed no abnormalities in the thyroid gland. The patient began thyroid hormone replacement with 75 μg/day levothyroxine. In parallel, an examination for her Cushingoid features revealed ACTH-dependent hypercortisolemia (Table 2A). Her urinary free cortisol excretion (214 μg/day, reference range: 11.2-80.3 μg/day) was high. Her morning plasma cortisol level was insufficiently suppressed by the oral administration of a low dose of dexamethasone, but it was appropriately suppressed following a high dose of dexamethasone (Table 2B). Dynamic tests for the secretion of pituitary hormones revealed a certain ACTH release to a corticotropin-releasing hormone (CRH) load, a reduced TSH response to a thyrotropin-

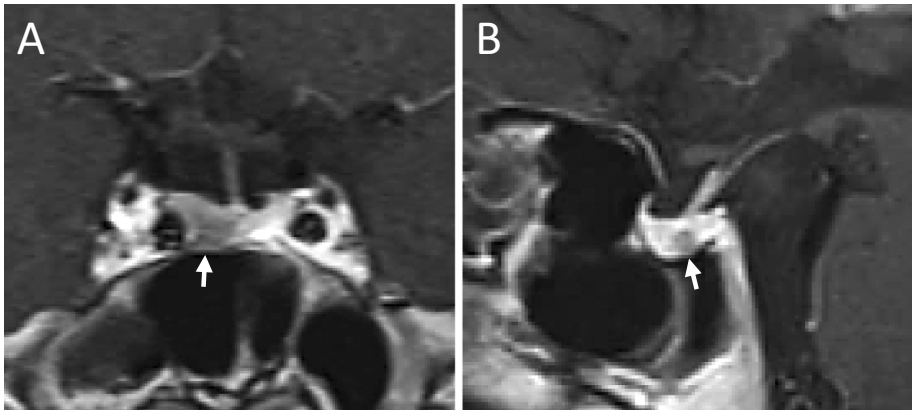

Figure 2. Magnetic resonance imaging of the pituitary gland (August 2011). Gadolinium-enhanced T1-weighted magnetic resonance imaging (A: coronal plane, B: sagittal plane) revealed a 0.5 cm tumor on the right side of the pituitary gland (arrows), and the hypophyseal stalk was observed to have slightly shifted to the left.

releasing hormone (TRH) load, and reduced growth hormone (GH) response to a growth hormone-releasing factor (GRF) load (Table 2C). The patient's serum insulin-like growth factor-1 (IGF-1) level (145 ng/mL, reference range: 100-250 ng/mL) was normal. MRI detected a 0.5 cm tumor in her pituitary gland (Fig. 2). These results indicated a diagnosis of Cushing's disease accompanied by central hypothyroidism, and additionally, a decreased release of GH due to hypercortisolemia was suspected.

The patient experienced specific decreases in her widespread muscle pain (visual analogue scale score: 4 of 10) without any change in the region and behavior of the pain during the course of levothyroxine replacement for her hypothyroidism. However, her mild neck weakness remained unchanged.

The patient underwent endoscopic transsphenoidal surgery in September 2011, and her pituitary tumor was completely removed. The histopathological features of the tumor were consistent with those of an ACTH-secreting pituitary microadenoma. The patient had undetectable basal plasma ACTH and cortisol levels after surgery, showed no ACTH or cortisol release to a CRH load, and received maintenance replacement therapy with 20 mg/day oral hydrocortisone. Because the patient's thyroid function was expected to improve, the levothyroxine replacement was discontinued just after surgery, and her basal serum thyroid hormone levels (TSH, 1.52 μU/mL; FT_3, 3.2 pg/mL; FT_4, 0.9 ng/dL) normalized by 3 months after surgery. Her Cushing's syndrome symptoms, including a rounded face, supraclavicular fat accumulation, and thin skin, resolved within 6 months after surgery, as did her neck muscle weakness (manual muscle testing score: 5 of 5). The patient experienced a decrease in her widespread muscle pain (visual analogue scale score: 3 of 10) without any change in the region and behavior of the muscle pain, during the 6 months after surgery. However, her spontaneous, pressure, and exercise pain in the muscles of the neck, chest, and extremities remained unresolved. The patient met the diagnostic criteria for fibromyalgia (Widespread Pain Index: 10 of 19 and Symptom Severity Scale score: 5 of 12) (1, 2).

Hydrocortisone replacement was discontinued in March 2013, and dynamic tests showed normal ACTH and cortisol release to CRH administration, but her GH release following GRF administration remained low (Table 2D). MRI performed in April 2013 revealed no abnormalities in the hypothalamus, hypophyseal stalk or pituitary gland, and no recurrence of pituitary tumors. Her serum IGF-1 level (90 ng/mL, reference range: 90-233 ng/mL) was low-normal in February 2015, and a growth hormone releasing peptide-2 load test showed a trend toward reduced GH release (Table 2E) (11), which was thought to be associated with fibromyalgia.

The patient had no recurrent Cushing's disease or hypothyroidism during the postoperative follow-up period of >4 years, but she suffered from prolonged fatigue, insomnia, and widespread muscle pain and was continuing treatment with oral analgesic drugs and sleeping pills for her persisting widespread myalgia and insomnia, respectively.

Discussion

In this case, the patient developed spontaneous, pressure, and exercise pain in the muscles of her neck, chest, and extremities along with fatigue and insomnia in the presence of Cushing's disease that was accompanied by central hypothyroidism. Her widespread myalgia remained unresolved for more than 4 years after successful pituitary surgery to treat Cushing's disease. The patient experienced a decrease in her muscle pain (visual analogue scale scores: from 6 to 3 of 10) during the recovery process from concomitant hypercortisolemia and hypothyroidism, but the region and behavior of her widespread myalgia remained almost completely unchanged during that period. These findings suggest that the patient developed fibromyalgia in association with concomitant untreated Cushing's disease and hypothyroidism, and the concomitant Cushing's disease and hypothyroidism also exacerbated her fibromyalgia.

There are some reported cases of fibromyalgia symptoms that occurred, possibly in association with relative adrenal insufficiency, after withdrawal of supraphysiological doses of exogenous steroids (6) or after adrenal surgery to treat primary adrenal Cushing's syndrome (8). An interesting case of severe fibromyalgia that occurred in association with hypopituitarism after a complete anterior hypophysectomy to treat Cushing's disease has been reported, in which a disturbed secretion of endogenous opioids and serotonin was also hypothesized to have triggered fibromyalgia (7). To our knowledge, our patient is the first reported case of fibromyalgia associated with untreated Cushing's syndrome. In our case, the central hypothyroidism caused by Cushing's disease may have played an important role in triggering and exacerbating fibromyalgia.

The mechanisms underlying the central hypothyroidism caused by Cushing's disease include mechanical compression of the hypophyseal stalk or pituitary gland by tumors (12), and suppression of TSH secretion by excessive cortisol levels (13), with or without non-thyroidal illness syndrome (14). A rare case of isolated TSH deficiency coincidentally associated with Cushing's disease has also been reported (15). Our patient had central hypothyroidism in the absence of any marked mechanical compression of the hypophyseal stalk or pituitary gland by the ACTH-secreting pituitary microadenoma (Fig. 2), and the hypothyroidism resolved after the patient underwent surgical treatment for Cushing's disease. Therefore, the central hypothyroidism of our patient was likely to have been caused by excessive cortisol production.

Hypothyroidism that induces reversible muscle pain and stiffness that is often associated with proximal muscle weakness is referred to as hypothyroid myopathy (16). On the other hand, hypothyroidism *per se* may exacerbate muscle pain in patients with fibromyalgia (3, 4). Our patient experienced decreased muscle pain during the 6 months of levothyroxine treatment before surgery to treat Cushing's disease with central hypothyroidism. She experienced a further decrease in her muscle pain during the 6 months after surgery. Taken together, these findings suggest that our patient might have had hypothyroid myopathy that resolved over a 1-year period in the absence of muscle weakness in the extremities and elevations of serum myogenic enzymes. At the same time, because the region and behavior of her widespread myalgia remained almost completely unchanged before and after the surgery, her hypothyroidism probably increased the widespread myalgia via the exacerbation of the fibromyalgia.

Cushing's syndrome can cause glucocorticoid-induced myopathy characterized by reversible proximal muscle weakness without pain (17). Our patient presented with neck muscle weakness that remained unchanged during the 6 months of levothyroxine treatment for hypothyroidism, but this resolved following treatment for Cushing's disease. Therefore, she may have had glucocorticoid-induced myopathy in the presence of Cushing's disease.

The patient's muscle biopsy specimen was obtained from the left biceps brachii muscle prior to receiving treatment for hypothyroidism and Cushing's disease and revealed nonspecific, chronic myogenic changes (Fig. 1). Such myogenic changes are often observed in patients with endocrine disorders, including both glucocorticoid-induced and hypothyroid myopathy (16), and may be found in patients with fibromyalgia (18). Because a microscopic examination was not performed again after treatment for Cushing's disease, the causal factors underlying the patient's myogenic changes remain unclear. However, the absence of muscle weakness in the extremities of our patient suggests that fibromyalgia was the most likely factor underlying the microscopic findings of chronic myogenic changes.

The patient showed a persistent trend toward decreased GH secretion even after undergoing surgical treatment for Cushing's disease (Table 2D). Additionally, although her ACTH and cortisol responses to CRH administration were found to be normal, she presented with mildly decreased basal plasma ACTH and cortisol levels without any morphological defects in the pituitary gland 1.5 years after the resolution of her Cushing's disease. These endocrinological alterations in and of themselves do not cause muscle pain, but some studies have suggested that patients with fibromyalgia demonstrate some alterations in the hypothalamic-pituitary endocrine function, including decreased GH, ACTH, and cortisol secretion (19-21). These changes may in turn enhance the symptoms of fibromyalgia (4, 5). Therefore, the altered pituitary function in the present patient may have borne a reciprocal relationship to fibromyalgia. A careful check of the pituitary function along with the clinical course of widespread muscle pain was therefore required in this case.

In conclusion, this case study describes a patient who developed fibromyalgia in association with untreated Cushing's disease and central hypothyroidism. The central hypothyroidism caused by Cushing's disease probably played an important role in triggering and exacerbating the fibromyalgia. Our case highlights the need to examine the endocrine function, including the pituitary, thyroid, and adrenal function, in conjunction with the assessment of characteristic physical findings, such as a Cushingoid appearance, in patients who present with muscle pain.

The authors state that they have no Conflict of Interest (COI).

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