NOTE

Multifocal Fibrosclerosis as a Possible Cause of Panhypopituitarism with Central Diabetes Insipidus

MASAHIKO KISHIMOTO, YASUHIKO OKIMURA, KEN-ICHI KIMURA*, ISHIKAZU MIZUNO, GENZO IGUCHI, MARIKO FUMOTO, YUTAKA TAKAHASHI, FUMIO KANDA, HIDESUKE KAJI, HIROMI ABE, KEISUKE HANIOKA** AND KAZUO CHIHARA

Third Division Department of Medicine, Kobe University School of Medicine, Kobe 650-0017, Japan
*Department of Neurology, Yodogawa Christian Hospital, Osaka 533-0032, Japan
**Department of Pathology, Kobe University School of Medicine, Kobe 650-0017, Japan

Abstract. Multifocal fibrosclerosis denotes a combination of similar fibrous disorders occurring at different anatomical sites. We encountered a 53-year-old male patient with orbital pseudotumor, chronic paranasal sinusitis, fibrous nodules of the lungs, intracranial pachymeningitis, and panhypopituitarism with central diabetes insipidus (DI) as a possible manifestation of multifocal fibrosclerosis. It has been reported that intracranial pachymeningitis or orbital pseudotumor associated with multifocal fibrosclerosis could invade the sella turcica causing a variety of anterior and/or posterior pituitary dysfunctions. In our case, intracranial pachymeningitis apparently involved the pituitary stalk and gland. Isolated gonadotropin deficiency, in addition to central DI, preceded panhypopituitarism. Although panhypopituitarism with central DI due to multifocal fibrosclerosis is quite rare and only one case has ever been reported, this systemic fibrotic disorder can be a possible cause of panhypopituitarism with central DI.

Key words: Multifocal fibrosclerosis, Panhypopituitarism, Central diabetes insipidus, Orbital pseudotumor, Intracranial pachymeningitis

MULTIFOCAL fibrosclerosis is a generic term used to denote a group of fibrosing conditions occurring at different anatomical sites. This disorder is of unknown etiology, although an immune process has been postulated, and occasionally steroids may result in some improvement [1]. Several manifestations such as orbital pseudotumor [2], retroperitoneal fibrosis [3], mediastinal fibrosis [3], pachymeningitis [4], Riedel's thyroiditis [5], sclerosing cholangitis [6], paranasal sinusitis [7], and pulmonary fibrosis [8] are reported. However, panhypopituitarism with central diabetes insipidus (DI) due to multifocal fibrosclerosis is quite rare and to our knowledge only one case has ever been reported [9]. We describe here another case of a 53-year-old male who showed panhypopituitarism with central DI associated with multifocal fibrosclerosis.

Case Report

A 53-year-old male patient was transferred to our hospital because of persistent headaches. The patient had no remarkable family or past history except appendicitis until 1992. In 1992, at age 47, he went to the Hyogo Adult Disease Center for consultation because he had noticed left exophthalmos. A left orbital pseudotumor was then pointed out, which was refractory to both steroid and radiation therapy. The tumor was surgically removed in 1994, and the resected retro-orbital fatty tissue histologically iden-
tified as chronic lobular panniculitis. Fat cells were largely replaced by markedly infiltrated lymphocytes and plasma cells with varying amounts of fibrosis (Fig. 1A). Inflammatory cell infiltration was also prominent around the blood vessels of the adipose tissue, but no tissue destruction associated with vasculitis was observed. There was no granuloma throughout the resected tissue. These findings suggested that a diagnosis of polyarteritis nodosa, Wegener's granulomatosis, or sarcoidosis was unlikely. In 1993, chronic paranasal sinusitis was detected. Histologic examination of the excised paranasal sinus tissue showed chronic non-specific inflammation with focal fibrosis. In 1996, bilateral pulmonary abnormal nodular lesions of unknown origin appeared. Neither antibiotics nor antituberculous agents was effective to change the size. Needle biopsy of the lung lesions revealed inflammatory granulation tissue consisting of infiltrated polymorphous cells and proliferated fibroblasts (Fig. 1B).

In 1997, polyuria and polydipsia appeared, and a thickened right tentorium cerebelli was found on magnetic resonance imaging (MRI) which was performed at the Hyogo Adult Disease Center. He was diagnosed as central DI, and was then started on a treatment with intranasal 1-desamino-8-D-arginine vasopressin (dDAVP) at the hospital. He was also given corticosteroids in the form of prednisolone 10 mg per day, and isoniazid and rifampicin for possible tuberculosis. On January 8, 1998, he was transferred to our hospital because of persistent headaches.

First admission to Kobe University Hospital

The general examination revealed no abnormal signs; blood pressure 140/80 mmHg, pulse rate regular at 80 bpm, and body temperature 36.6°C. Neurologically he showed disturbed movement of the left eyeball, which had appeared after the operation for orbital pseudotumor. MRI disclosed an enhancement of the thickened right tentorium cerebelli on post gadolinium(Gd)-enhanced T1-weighted axial imaging (Fig. 2A).

Laboratory test findings involving anti-nuclear antibody, anti-neutrophilic cytoplasm antibody,

![Fig. 1. A: Histological appearance of the orbital pseudotumor. Adipose tissue was replaced by fibrosis and infiltrated inflammatory cells. B: Needle biopsy from lower lobe of left lung under guide using computed tomography. Needle core consisted of inflammatory granulation tissue with active proliferation of fibroblasts.](image_url)
PITUITARY DYSFUNCTION ASSOCIATED WITH MULTIFOCAL FIBROSCLEROSIS

rheumatoid factor, complement level, lysozyme, angiotensin converting enzyme, candida antigen, aspergillus antigen, cryptococcus antigen, anti-HIV antibody, and serology for syphilis were all normal or negative except for an erythrocyte sedimentation rate (ESR) of 22 mm/hr and C-reactive protein (CRP) of 4.0 mg/dl.

Lumbar puncture revealed an opening pressure of 170 mmH2O with clear, colorless, acellular CSF. The CSF protein was 51 mg/dl, and CSF glucose was 56 mg/dl with a plasma glucose level of 89 mg/dl. Aggressive evaluation for tuberculosis was also performed with no positive result.

He was at that time diagnosed as intracranial pachymeningitis of unknown origin. Headaches resolved spontaneously, and he was followed as an outpatient receiving prednisolone 7.5 mg per day, intranasal dDAVP, and antituberculous agents.

During this admission, pituitary function was also assessed (Table 1 and Fig. 3). MRI revealed abnormalities of the pituitary; Gd-enhanced T1-weighted MRI showed mosaic image of the pituitary gland and swelling of the pituitary stalk with disappearance of the high intensity of posterior lobe (Fig. 2B). Basal gonadotropin levels were low, LH 0.6 mIU/ml and FSH 2.0 mIU/ml. Plasma testosterone was also low, 0.1 ng/ml, although he had normal pubic hair, sexual desire, and erectile function. Because of the morphological abnormality of the pituitary gland in MRI, his hypopituitarism was first suspected to be

![Fig. 2. T1-weighted MRI images on first admission. A: axial view, enhanced with gadolinium (Gd); thickened right tentorium cerebelli was observed. B: sagittal view, enhanced with Gd; heterogenously enhanced pituitary with thickening of pituitary stalk was observed. High intensity of posterior lobe was not seen.](image)

| Table 1. Responses of pituitary and adrenal hormones to intravenous injection of GHRH (50 μg), CRH (100 μg), and TRH (500 μg) during first and second admission. |
|---|---|---|---|---|---|
| Time (min) | 0 | 30 | 60 | 90 | 120 |
| GH (ng/ml) first admission | 1.2 | 15.8 | 12.5 | 7.9 | 3.9 |
| GH (ng/ml) second admission | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 |
| TSH (μU/ml) first admission | 1.4 | 8.3 | 7.6 | 5.4 | 4.0 |
| TSH (μU/ml) second admission | 2.2 | 3.7 | 3.0 | 2.8 | 2.5 |
| PRL (ng/ml) first admission | 7.5 | 15.9 | 14.7 | 12.2 | 9.6 |
| PRL (ng/ml) second admission | <0.5 | 0.5 | 0.5 | <0.5 | <0.5 |
| ACTH (pg/ml) first admission | 80.9 | 73.5 | 67.8 | 58.4 | 43.3 |
| ACTH (pg/ml) second admission | <4 | <4 | <4 | <4 | <4 |
| Cortisol (μg/dl) first admission | 7.8 | 12.1 | 10.0 | 9.4 | 7.7 |
| Cortisol (μg/dl) second admission | 0.5 | 0.5 | 0.4 | 0.3 | 0.4 |
primary. However, repetitive LHRH injections improved the responses of LH and FSH (Fig. 3), suggesting the existence of secondary, rather than primary, hypopituitarism. Consistent with the diagnosis of central DI, at the end of the overnight water deprivation test, plasma osmolality increased to 304 mOsmol/kg H2O with a low urinary osmolality (122 mOsmol/kg H2O) and a low plasma level of antidiuretic hormone (ADH) (0.41 pg/ml). Intranasal dDAVP, 10 μg/day, controlled DI in good condition during and after the first admission.

Second admission to Kobe University Hospital

On August 13, 1998, he was admitted to our hospital again due to general fatigue. Movement of the left eye was still disturbed, but other neurological and general findings were normal.

Laboratory data obtained on admission are shown in Table 2. CRP levels were markedly elevated, and chest X-ray film revealed an increase in nodular shadows detected in the right upper and left lower lung fields (Fig. 4A, B). Anti-neutrophilic cytoplasm antibody, candida antigen, aspergillus antigen, and cryptococcus antigen test results were all normal or negative as at first admission. Intensive examinations ruling out tuberculosis were also performed which did not show any positive results. No bacteria were detected in the sputum.

Steroid pulse in the form of intravenous hydrocortisone 400 mg x 1 day and 200 mg x 4 days were given. Corticosteroid treatment resulted in dramatic improvement of nodular shadows (Fig. 4C) and decreased CRP levels from 38.4 mg/dl to 0.7 mg/dl on August 21.

Pathological findings and clinical course, as mentioned above, led us to consider systemic fibrotic disease, first described by Barrett in 1958 [10] and named multifocal fibrosclerosis by Comings et al. in 1967 [11], as a cause of orbital pseudotumor, chronic sinusitis, fibrous nodules of the lungs, pachymeningitis, and hypopituitarism with central DI in this patient. Antituberculous agents were stopped on August 25. Thereafter the pulmonary shadows did not worsen (Fig. 4D).

Pituitary function was assessed again on September 10, when 15 mg prednisolone had been given after the cessation of intravenous administration of hydro-
cortisone for 5 days. ACTH, GH, LH, FSH, and PRL showed no response to CRH, GHRH, TRH, and LHRH administration. Plasma TSH levels registered a minor increase in response to TRH (Table 1 and Fig. 3).

It was, therefore, concluded that the activity of multifocal fibrosclerosis had increased and that while the corticosteroids had resulted in improvement of the pulmonary lesions, they were not effective for the pituitary involvement judging from the decreased responses of pituitary hormones to CRH, GHRH, TRH, and LHRH. Secondary hypothyroidism might be one of the reasons for general fatigue. At discharge, he was receiving prednisolone 15 mg/day, levothyroxine 50 µg/day, and intranasal dDAVP 10 µg/day. During and after admission, DI was well controlled with intranasal dDAVP.

**Discussion**

As early as 1958, Barrett suggested that orbital pseudotumor, mediastinal and retroperitoneal fibrosis, and Riedel's thyroiditis had similar pathological features [10]. This systemic fibrotic disease was named multifocal fibrosclerosis by Comings et al. [11]. Until now, several clinical manifestations are reported such as orbital pseudotumor [2], mediastinal fibrosis [3], retroperitoneal fibrosis [3], Riedel's thyroiditis [5], Dupuytren's contracture [11], intracranial pachymeningitis [4], sclerosing cholangitis [6], paranasal sinusitis [7], pulmonary fibrosis [8], testicular fibrosis [12], and subcutaneous fibrosis [13]. In addition, intracranial pachymeningitis or orbital pseudotumor can invade the sella turcica to accompany varying degrees of pituitary dysfunction, ranging from isolated gonadotropin deficiency [14, 15] to panhypopituitarism with [9] or without central DI [16], although the incidence is rare and the pituitary function is not always impaired [7].

In our patient, intracranial pachymeningitis had invaded the pituitary stalk and gland, leading to panhypopituitarism. During the first admission, assessment of the patient's pituitary function established that LH and FSH responses to LHRH were blunted, although the basal secretion of ACTH and the responses of other pituitary hormones were preserved. The blunted response of LH and FSH were partially recovered by the repetitive administration of LHRH. These findings suggested that the lesion was located in the hypothalamus and/or pituitary stalk. MRI showed thickening of the right tentorium cerebelli in 1997 and thickening of the pituitary stalk in addition to the tentorium lesion in 1998. Since the pituitary stalk penetrates the diaphragma sellae above the sella turcica, it is likely that pachymeningitis invaded the diaphragma sellae the pituitary stalk.

During the second admission, the provocative test for pituitary hormones did not show any increase in plasma ACTH, GH, and PRL in addition to LH and FSH. This suggested the worsening of the pituitary
function probably due to the involvement of the pituitary gland in addition to the pituitary stalk or hypothalamus. If the pituitary is intact, PRL response should not be blunted, but should be enhanced, since PRL secretion is mainly regulated by dopamine, an inhibitory hypothalamic hormone. Actually, in our case, PRL response to TRH was completely blunted, suggesting, at least in part, direct involvement of the pituitary gland. In this context, the blunted responses of GH and TSH also appeared to be due to the invasion of multifocal fibrosclerosis to the pituitary gland.

However, the possibility remains that exogenous glucocorticoids might have suppressed the secretion of pituitary hormones, since the provocative test was performed 24 days after intravenous administration of hydrocortisone and during oral administration of prednisolone, although prednisolone was discontinued on the test day. We continued to prescribe a maintenance dose of prednisolone in view of the risk of exacerbating the disease process without it. However, the total amount of hydrocortisone was not so large as the dose used in usual steroid pulse therapy, and prednisolone was given during the first admission as well. Therefore, we consider the results of the two series of provocative tests to be comparable.

Lymphocytic adenohypophysitis (LAH) was ruled out in this case, since it is usually confined to the anterior pituitary [17] and not associated with fibrosclerotic lesions in other organs. It is predominantly seen among females and commonly affects young women during late pregnancy or in the postpartum period [17]. However, DI cases with LAH have been increasingly reported [18, 19].

Lymphocytic infundibulo-hypophysitis (LIH) is another possibility, but anterior pituitary hormone deficiency observed in our patient is quite unusual among LIH patients [20, 21]. There is a report of two cases presenting with both anterior pituitary dysfunction and DI, which the authors called "necrotizing infundibulo-hypophysitis" [22]. However, the two cases were not associated with multiple fibrous disorders seen at different anatomical sites in our

PITUITARY DYSFUNCTION ASSOCIATED WITH MULTIFOCAL FIBROSCLEROSIS

Patient. Other disorders, such as sarcoidosis, malignant lymphoma, and Langerhans cell histiocytosis are unlikely considering the pathological findings of orbital, paranasal sinus, and pulmonary lesions.

Finally, multifocal fibrosclerosis is the most likely diagnosis for our case, as it results from abnormal immune process, and glucocorticoid is effective in some cases. In such diseases based on immune disorder, cell type-specific dysfunction might occur. With respect to this point, Grossman [15] reported an interesting case with isolated gonadotropin deficiency. Their case is very similar to ours in that isolated gonadotropin deficiency occurred, although they did not describe the course of the disease. However, a previous report indicated a case in which lymphocytic hypophysitis was associated with multifocal fibrosclerosis [23]. Therefore, it remains to be clarified whether multifocal fibrosclerosis may share some pathogenesis with other disorders, such as LAH with DI, or "necrotizing infundibulo-hypophysitis".

Although an immune process in the pathogenesis of multifocal fibrosclerosis has been postulated, steroid therapy is not uniformly successful. As in our case, different lesions showed different reactions to steroids even in the same patient, which cannot be explained by organ specificity. For example, in some cases steroids were effective for Reidel's thyroiditis [24], while in other cases it was not [25]. We hypothesize that the effectiveness of steroids may be diminished by the progression of fibrosis.

In summary, we described the second case of panhypopituitarism with central DI as a rare but possible manifestation of multifocal fibrosclerosis in addition to orbital pseudotumor, chronic paranasal sinusitis pulmonary fibrotic lesions, and intracranial pachymeningitis.

References

18. Koshiyama H, Sato H, Yorita S, Koh T, Kanatsuna T, Nishimura K, Hayakawa K, Takahashi J, Hashi-


