Primary Pituitary Lymphoma Presenting as Hypophysitis

YU-YAO HUANG, SHU-FU LIN, PO DUNN*, YU-YU WAI**, CHUEN HSUEH*** AND JIR-SHIONG TSAI#

Division of Endocrinology and Metabolism, Department of Internal Medicine, Chang Gung Memorial Hospital and University, Gueishan, Taoyuan 333, Taiwan
*Division of Hematology, Department of Internal Medicine, Chang Gung Memorial Hospital and University, Gueishan, Taoyuan 333, Taiwan
**Department of Radiology, Chang Gung Memorial Hospital and University, Gueishan, Taoyuan 333, Taiwan
***Department of Pathology, Chang Gung Memorial Hospital and University, Gueishan, Taoyuan 333, Taiwan
#Sun Yat-Sen Cancer Center, Taipei 112, Taiwan

Abstract. A 47-year-old man had suffered from prolonged fever for two months without clinical evidence of infection. Blood biochemistry and endocrine dysfunction indicated that he had pituitary insufficiency. Thorough whole body imaging studies merely identified a 22 × 14 mm mass lesion in the sella turcica. Tumor pathology and special cell marker study revealed the infiltration of atypical T-lymphoid cells and concomitant presence of some B-lymphoid cells. The fever subsided gradually following subtotal tumor resection and steroid supplementation. However, the mass lesion had invaded the cavernous sinus and optic chiasma shortly after surgery. Six months after his initial visit, metastasis lesions in the liver, the left adrenal gland, and retroperitoneal lymph nodes were discovered. In contrast to cells in the pituitary, the pathological investigation of the liver mass confirmed it to be exclusively of T-cell origin. Therefore, it is plausible that the pituitary dysfunction was related to an inflammatory process, namely hypophysitis, as well as the T-cell lymphoma. This case exemplifies the rarely noted condition of primary pituitary lymphoma with concomitant hypophysitis. Clinical diagnosis is indiscernible until the occurrence of systemic tumor metastasis.

Key words: Systemic lymphoma, Hypopituitarism, Lymphocytic hypophysitis, Fever of unknown origin

PITUITARY insufficiency in adulthood is usually secondary to pituitary or hypothalamic space-occupying lesions, pituitary surgery, or prior extracranial radiation. Discrimination among the etiologies of a mass in the sella is broad in scope, including adenomas, cysts, granulomatous inflammation, autoimmune diseases, primary or metastatic neoplasms, aneurysms and parasellar lesion [1, 2]. The differential diagnosis of a sellar mass in a patient presenting with fever includes apoplexy or leakage of necrotic materials from a benign tumor or cyst [3–5]. More rarely, fever from a pituitary abscess has been reported [6]. Recently, Landman et al. observed a case of pituitary lymphoma manifesting as a fever of unknown origin [7]. This study reported a case with a primary pituitary lymphoma (PPL) displaying fever and hyponatremia as his cardinal symptoms. The diagnosis was determined following occurrence of systemic metastasis.

Case Study

A 47-year-old man had been in his usual state of “good” health except for a decreased libido for four months prior to his admission for assessment of an unknown source of fever. He denied substance abuse and showed no history of exposure to anyone with a feverish condition. The patient had initially suffered from shaking chills preceding feverish feeling and a spiking temperature usually associated with night
sweats two months before hospitalization. The patient claimed a daily febrile episode, usually in the early morning of as high as 39.3°C and lasting for approximately an hour. He denied notable weight loss during that period. He was 173 cm tall, weighing 73 kg. His blood pressure was 96/56 mmHg, and pulse rate was 102 beats/min on admission. The border of the liver was palpable 3 cm below the right costal margin, spanning 15 cm. The spleen spanned 12 cm along the posterior axillary line in the right decubitus position. No palpable lymph node was discovered. His axillary and pubic hairs were preserved, and no neurological deficit appeared.

Laboratory studies showed pancytopenia (red blood cells \(2.2 \times 10^{11}/\mu L\), hemoglobin 7.0 g/dL, reticulocytes 4.5%, white blood cells \(2.6 \times 10^{9}/\mu L\) with 56% neutrophils, 20% lymphocytes, 20% monocytes, 4% eosinophils, and platelets \(78 \times 10^{9}/\mu L\)). Liver chemistry was within normal range apart from a positive serology test for hepatitis B virus (HBsAg positive, HBsAb positive and HBeAg negative). The serum level of C-reactive protein was 13.45 mg/L (normal, <5 mg/L). The serum lactate dehydrogenase (LDH, 404 IU/L; normal, 47–140 IU/L) and \(\beta_2\)-microglobulin (4411 \(\mu g/L\); normal, 800–2400 \(\mu g/L\)) were significantly above normal range. Other serological parameters, cultures of the blood, urine, stool and results of cerebrospinal fluid were unrevealing.

Abdominal and pelvic computed tomography (CT) displayed no focal abnormal lesions except for hepatosplenomegaly. The pathological findings of the randomized liver biopsy specimen showed minimal portal inflammation. Bone marrow histology from right iliac crest biopsy verified all cell lineages were normal.

Significant hyponatremia (sodium of 115 mEq/L) was found. Extended hormonal studies showed pituitary malfunction. Table 1 displays the very low levels of ACTH and FSH. The serum levels of TSH and LH were undetectable. Serum levels of T4, T3, cortisol, and testosterone were extremely low. Stimulation tests with GnRH (0.1 mg iv bolus) and TRH (0.5 mg iv bolus) revealed poor responsiveness of gonadotrophs and thyrotrophs (Table 1). The hypopituitarism might have contributed to his hyponatremia. A pituitary CT image disclosed a homogeneous enhanced pituitary mass (22 × 14 mm), with the sella turcica slightly widened, and without bony destruction (Fig. 1a).

The patient underwent a trans-sphenoidal pituitary tumor subtotal resection. Fig. 2a shows that the pituitary tumor was principally comprised of atypical lymphoid cells. The infiltrating lymphocytes appeared to be small with irregular nuclear membrane. Immunohistochemical studies displayed the main component of the CD3-positive T-lymphoid lineage (Fig. 2b). However, a substantial amount of CD20-positive B-lymphoid cells was also observed (Fig. 2c). The pathological results were not confirmatory for either T or B cell lymphoma. Thus we suggested that the lesion

<table>
<thead>
<tr>
<th>Table 1. Summary of endocrinological examination at initial presentation, at presentation of left ptosis, and 8 weeks following brain irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial presentation</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>ACTH</td>
</tr>
<tr>
<td>FSH</td>
</tr>
<tr>
<td>p-FSH</td>
</tr>
<tr>
<td>LH</td>
</tr>
<tr>
<td>p-LH</td>
</tr>
<tr>
<td>TSH</td>
</tr>
<tr>
<td>p-TSH</td>
</tr>
<tr>
<td>PRL</td>
</tr>
<tr>
<td>p-PRL</td>
</tr>
<tr>
<td>GH</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>cortisol</td>
</tr>
<tr>
<td>testosterone</td>
</tr>
</tbody>
</table>

p-: indicates the peak responsive level of hormone after stimulation test of GnRH or TRH.
contained lymphocytic penetration in reaction to an inflammatory process. It was therefore considered that the space-occupying lesion inside the sella turcica was lymphocytic hypophysitis.

Empiric hydrocortisone was administered before the neurosurgical approach. Following surgery, this patient sustained hormonal replacement with cortisol acetate (37.5 mg/day) and thyroxine (50 µg/day). Fig. 3 summarizes the clinical course by addressing the symptoms and treatments. He became defervescent three weeks later. Six weeks after surgery, the patient suffered ptosis of the right eye and diplopia because of neurological deficits of right cranial nerves III and VI. In addition, bilateral superior temporal visual defects were discovered on a visual field examination. A subsequent sellar magnetic resonance imaging (MRI) revealed a pituitary tumor extending upwards, compressing the optic chiasma, and affecting the right cavernous segment (Fig. 1b). Because the patient rejected further surgery of the pituitary mass, prednisolone was administered (30 mg/day) to possibly curtail the inflammatory progression. The diplopia and right ptosis gradually improved within three months. However, this patient developed ptosis of the other eye five months after initial presentation (Fig. 3). This ptosis was due to palsy of left cranial nerves III and VI consequent upon tumor invasion of the left cavernous sinus (Fig. 1c). Increased prednisolone appeared only to achieve a partial and temporary response by the sellar tumor.

Six months after his first visit, this patient experienced remittent high fever connected with chills and night sweats. Repeat abdominal CT scan identified three hepatic tumors, a large left adrenal tumor, and multiple enlarged retroperitoneal and hilar lymph nodes (Fig. 4a). Again, an echo-guided liver biopsy revealed infiltration of atypical small lymphoid cells with uneven nuclear membranes (Fig. 2d). The im-

Fig. 1. Serial imaging examinations of the pituitary gland. a) Initial coronal CT with contrast revealed fullness of the pituitary sella with upward bulging of the diaphragm of the sella, identifying a pituitary mass. b) Coronal T1-weighted MRI of the sella showed a bulging of the right cavernous sinus with expanded soft tissue at the lateral aspect of the carotid artery (arrow). c) Coronal T1-weighted MRI demonstrating markedly reduced size of the soft tissue mass in the right cavernous sinus and pituitary fossa, but another mass emergent in the left cavernous sinus (arrow). d) Coronal T1-weighted MRI disclosed the sellar mass had decreased in size. The left cavernous sinus involvement was improved in comparison with (c).
munoistochemical study was positive for T lymphocytes, as shown by CD3 (Fig. 2e), CD5, and CD8. However, the stain of CD20 (Fig. 2f), CD4, CD56 and cyclin D1 were negative. Since the morphological features of lymphoid cells were comparable between the tumor in the pituitary and that in the liver, primary
pituitary T cell lymphoma with systemic metastasis was diagnosed. A repeat bone marrow biopsy again demonstrated normal appearance of marrow cells. The cerebrospinal fluid cytology revealed no proof of lymphoma involvement.

This patient received an intrathecal methotrexate injection (15 mg) every three days for five times; conventional radiotherapy of 2400 cGy/12 fraction to the entire brain, boosted to 4000 cGy/20 fraction to the pituitary tumor; and systemic chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP regimen). The fever diminished soon after treatment began, and the left ptosis and diplopia recovered gradually. The patient continued chemotherapy with the CHOP regimen every three weeks, and a succeeding sellar MRI (Fig. 1d) and abdominal CT (Fig. 4b) depicted significant tumor reduction following multi-regimen therapy for five months.

During the course, the patient had no symptom of polyuria and his urine gravity examinations were maintained within the reference range. As shown in the Table 1, the elevation of FSH/LH and TSH levels, observed while the patient was having extrapituitary invasive tumor, suggests the responsiveness of hypophysitis under steroid treatment.

**Discussion**

A case was presented of PPL concomitant with hypophysitis. The cardinal manifestation was remittent high fever. Following detailed examination, a pituitary mass and elevated serum \( \beta_2 \)-microglobulin and LDH were discovered. The pathologic identification was indefinite owing to the presence of both T cells and B lymphocytes in the pituitary tumor. Not until the intra-abdominal metastasis was observed six months later was the T-cell lymphoma diagnosed.

Approximately 19%–53% of patients with non-Hodgkin’s lymphomas manifest fever, night sweats, and/or body weight loss as classic B symptoms [8]. Patients with lymphomas infrequently present with fever as the principal symptom without advanced disease. The B symptoms and high levels of surrogate tumor markers, serum LDH and \( \beta_2 \)-microglobulin, make possible a tumor positioned in some unrevealed anatomical site other than the pituitary. Because extrapituitary lymphoma was not initially identified via thorough tumor work-up, a primary lymphoma of the pituitary gland remains the best explanation. Landman et al. reported a PPL presenting with high fever in which the serum LDH and \( \beta_2 \)-microglobulin were very high [7].

Bloomfield et al. [9] claimed a strong correlation between cytopenia and bone marrow involvement in non-Hodgkin’s lymphoma. Bone marrow studies of the patient in the present study indicated all cell lineages were normal while the tumor was confined to the pituitary and in the stage of extensive metastasis. The pancytopenia in this patient might not have been directly linked to bone marrow involvement of lymphoma. Alternatively, it might be caused by divergent factors such as increased sequestration of blood cells in the enlarged spleen, hypocortisolemia, hypothyroidism...
and chronic disease connected with persistent fever.

The presence of B lymphoid cells in the primary tumor hindered the diagnosis of primary T cell lymphoma. In the literature, sporadic cases of pituitary lymphoma have been observed to possess variable inflammatory alterations. Singh et al. [10] described an instance of pituitary invasive mass. The pituitary biopsy revealed “chronic inflammation” and their patient was found to have non-Hodgkin’s lymphoma in the right inguinal lymph node six months later. Giustina et al. [11] noted a case of T-cell pituitary lymphoma, in addition to tumor cells, with infiltration of plasma cells, neutrophils, and eosinophils. The present work is the first to demonstrate coexisting B and T lymphocytes in the primary pituitary T cell lymphoma. It is notable that in primary thyroid lymphoma, coexisting Hashimoto’s thyroiditis has been more commonly emphasized [12–14]. It was hypothesized that lymphoma cells inside the thyroid could be transformed from lymphocytes during chronic inflammatory process [11–14]. Whether primary non-Hodgkin’s lymphoma in endocrine tissue carries greater chance with coexisting lymphocytic inflammation remains uncertain.

Lymphocytic hypophysitis alone sometimes can manifest fever. However, most described cases of lymphocytic hypophysitis with fever presented meningeal signs [15, 16]. The absence of meningeal sign in the present patient might exclude the likelihood of fever directly resulting from lymphocytic hypophysitis. Adrenal insufficiency might cause fever which dramati-
cally responds to corticosteroid supplements [17, 18]. Remission of fever in the present patient was not closely connected with the corticosteroid treatment in the first admission. Instead, the fever diminished soon after multi-regimen therapy for an extensive T lymphoma, implying that tumor fever was most likely.

The invasive nature of pituitary tumors is not restricted to malignancy. Nussbaum et al. [19] reported a 40-year-old man with lymphocytic hypophysitis and recurrent bilateral cavernous sinus involvement. The incidence of cavernous sinus invasion is estimated to be 31% in PPL [11] and 6% in lymphocytic hypophysitis [20]. However, PPL is often more aggressive and may extend to the sphenoid sinus, the cavernous sinus, or the floor of the third ventricle. In contrast, lymphocytic hypophysitis is usually limited to the sellar or parasellar area. The usage of steroid might constrain the local extension of both lymphoma and hypophysitis.

It is generally believed that conservative management is appropriate in the majority of patients with lymphocytic hypophysitis since spontaneous resolution of both the mass and the hypopituitarism has been reported [20–23]. However, the experience of this case implies that a diagnosis of lymphocytic hypophysitis from PPL is challenging. Thus, when a pituitary lymphoma is combined with inflammatory alteration, the lymphoma may be indistinguishable from lymphocytic hypophysitis. Clinicians should be alert to this possibility.

References


