Intravascular Large B-cell Lymphoma with Preceding Syndrome of Inappropriate Secretion of Antidiuretic Hormone

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Abstract

Intravascular large B-cell lymphoma (IVL) is a rare subtype of B-cell lymphoma presenting with neurological and dermatological lesions in addition to generalized symptoms such as fever and malaise. It may also be associated with variable manifestations of affected organs due to extranodal progression predominantly in the lumen of the small vessels. Here, we report a case of IVL with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as the sole manifestation at the initial presentation. The present case suggests that hormonal disturbances may progress in advance in IVL, before generalized symptoms develop.

Key words: intravascular large B-cell lymphoma, syndrome of inappropriate secretion of antidiuretic hormone

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Introduction

IVL is a rare type of non-Hodgkin lymphoma mostly observed in adults. This lymphoma is usually disseminated in extranodal sites at presentation, and the symptoms are highly variable. Among the various symptoms, neurological symptoms and skin lesions are relatively common. An Asian variant of IVL, characterized by hemophagocytosis, disseminated intravascular coagulation (DIC) and hepatosplenomegaly in the absence of neurological abnormalities, skin lesions, lymphadenopathy and a mass formation was proposed as a distinct disease entity (1). In either the classical or Asian variant of IVL, no distinctive epidemiological features have been identified based on the small number of cases reported in the literature (2). The clinical manifestations of hormonal disturbances have not been well documented either. The present case, diagnosed with SIADH-induced hyponatremia with disturbance of consciousness, was found by post-mortem studies to be a classical, non-Asian variant type IVL. This implies hormonal abnormalities alone can develop before other manifestations progress in IVL.

Case Report

A 75-year-old man was found to have hyponatremia (123 mEq/l) and elevated lactate dehydrogenase (LDH, 892 IU/l) in early August 2005, at a surgery outpatient clinic when the patient visited for a regular follow-up from a right hemicolectomy for an ascending colon carcinoma two years earlier. A left adrenal tumor 3 cm in diameter was noted by a computed tomographic (CT) scan (Fig. 1), and a week later the patient was admitted to the hospital for further evaluation of hyponatremia and elevated LDH. No abnormal finding was noted on physical examination but low blood pressure (84/60 mmHg). There was no skin lesion. Neurological examination showed no abnormalities except for a slight disturbance of consciousness (E4V4M6 at Glasgow coma scale). Performance status for the ECOG scale was 3 and there were no B symptoms. Although no marked peripheral cytopenia was noted initially (white blood cells 4,000/μl, he-
moglobin 11.2 g/dl, platelets 174×10³/μl), blood counts decreased gradually over a week (white blood cells of 2,400/μl, hemoglobin of 10.7 g/dl, and platelets of 105×10³/μl). The serum values of sodium, albumin, LDH and C-reactive protein on admission were 116 mEq/l, 2.8 g/dl, 853 IU/l and 7.46 mg/dl, respectively. The urine sodium level and osmotic pressure were normal, and the secretion of antidiuretic hormone was also normal (1.9 pg/dl: normal range 0.3-3.5 pg/dl). The hormonal levels, including adrenocorticotropic hormone (ACTH), cortisol, aldosterone, adrenaline, noradrenaline, dopamine, thyroid-stimulating hormone (TSH) and thyroid hormones, were normal, indicating that the function of the hypothalamic-pituitary-adrenal system, renin-angiotensin-aldosterone, and thyroid gland were normal. Therefore, a diagnosis of SIADH was made. The hormonal tests also revealed that the left adrenal tumor noted by a CT scan (Fig. 1) was non-functional. No intracranial lesion was noted by a head CT scan.

Drowsiness, low blood pressure and hyponatremia were improved by water restriction, hypertonic saline infusion, and administration of furosemide and fludrocortisone acetate. However, on day 13 after admission, pneumonia developed and did not improve despite administration of intravenous antibiotics. A bone marrow biopsy and an aspirate on day 18 for evaluation of pancytopenia failed to reveal abnormalities except for hypocellularity. There was no clear evidence of hemophagocytosis. Immunohistochemical staining of biopsy specimens for CD20 and CD79a was negative. Marrow differential cell counts are shown in Table 1. All thirteen metaphases analyzed showed normal karyotypes. Laboratory data on day 21 revealed elevated levels of ferritin (2,500 ng/ml), soluble interleukin-2 receptor (sIL-2R, 3,860 IU/ml) and β2-microglobulin (4.8 mg/l) in the patient’s serum. Multiple organ failure and DIC developed, and the patient died on day 28. A CT scan on the same day disclosed bilateral pleural effusion with bilateral pulmonary infiltrates, para-aortic and bilateral axillary lymph node swelling (Fig. 2a, b), and a subcutaneous tumor in the right clunis, in addition to the left adrenal tumor which was previously noted.

Permission for an autopsy, excluding the cerebrospinal

Figure 1. Abdominal CT before admission. A left adrenal tumor 3 cm in diameter was noted.

![Image](62x308 to 275x468)

Figure 2. CT images of the chest and abdomen on day 28 after admission. a. Consolidations and pleural effusion in bilateral lungs were noted. b. A CT scan with contrast materials revealed multiple swellings of abdominal para-aortic lymph nodes.

Table 1. Bone Marrow Differential Cell Count

<table>
<thead>
<tr>
<th>Nucleated cell count (NCC)</th>
<th>7,000 / μl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megakaryocytes</td>
<td>0 / μl</td>
</tr>
<tr>
<td>Blasts</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Promyelocytes</td>
<td>0%</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>6.4%</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>1.6%</td>
</tr>
<tr>
<td>Band neutrophils</td>
<td>27.2%</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>16.6%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>28.8%</td>
</tr>
<tr>
<td>Kosinophils</td>
<td>6.6%</td>
</tr>
<tr>
<td>Basophils</td>
<td>1.0%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2.4%</td>
</tr>
<tr>
<td>Macrophages</td>
<td>0.6%</td>
</tr>
<tr>
<td>Erythoblasts</td>
<td>7.2%</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>0%</td>
</tr>
</tbody>
</table>

Note: Possible hemorrhage cannot be ruled out, given the NCC and proportion of neutrophils. The biopsy showed moderate hypocellularity with normal ME ratio and a slightly decreased number of megakaryocytes.
system, was granted. The autopsy revealed atypical lymphocytes infiltrating into blood vessels of multiple organs including the liver (Fig. 3a and 3b), lung (Fig. 3c and 3d), adrenal glands (Fig. 3e and 3f), kidneys, stomach, gallbladder, thymus and prostate, with diffuse alveolar damage and acute renal tubular necrosis due to tumor embolism. Swelling of the liver hilar lymph nodes and para-aortic nodes was also noted. The CD20 and CD79a-positive atypical lymphocytes were mostly limited to the lumen of small blood vessels and sinusoids, which were compatible with IVL. CD3, CD5, CD10 and Bcl-2 were all negative for these atypical lymphocytes. There was no finding of hemophagocytosis in any organ including the bone marrow. No recurrence of the ascending colon carcinoma was observed. Incidental papillary carcinoma of the left thyroid lobe was found.

**Discussion**

Symptoms of IVL are highly variable as a result of the occlusion of small vessels by lymphoma cells in the involved organs. Neurological symptoms and skin lesions are the predominant manifestations, as originally described (2). In addition, patients with IVL show nonspecific clinical presentations, including fever and malaise, which presumably are attributed to inflammatory cytokines (3). Japanese cases which lack neurological and dermatological manifestations but have hemophagocytic syndrome (HPS) have been described and considered an Asian variant of IVL (1). IVL in general presents with widely disseminated extranodal sites, including bone marrow (2). The absence of lymphadenopathy and tumor formation makes its diagnosis difficult in most cases.

Given the nature of the systemic disease of IVL and its
angiotropic progression, it may cause endocrine disorders, but its association with these has been unclear because of the rarity of the disease. Although epidemiologic studies have not been available, anecdotal cases in the literature indicate that the adrenals seem to be the most frequently affected organ in terms of tumor formation in IVL and its Asian variant (1, 4). Hormonal insufficiency has been observed as a result of IVL involvement rather than hyperfunction; hypopituitarism (5-7), adrenal insufficiency (8-11) and SIADH (12) have also been documented.

Hypercytokinemia is one of the factors that can cause SIADH. Several cytokines such as interleukin (IL)-2, sIL-2R, IL-6, IL-1β and tumor necrosis factor (TNF)-α have been reported to stimulate the aberrant secretion of ADH by parvicellular and magnocellular neurons. For instance, there is evidence that intravenous administration of IL-6 triggers secretion of ADH (13). The concurrent development of HPS and SIADH in some cases of hematological malignancies also supports the role of cytokines in the development of SIADH (14-16). In the present case, HPS was not evident; however, the elevated serum level of sIL-2R indicated activation of T and B cells and a presumably hypercytokine state. Pathological findings for the pituitary gland were not clear in the present case because permission for an autopsy involving the cerebrospinal system was denied by the family. Immunohistochemical studies of the patient failed to show ADH production by lymphoma cells (data not shown), suggesting that ectopic ADH secretion was unlikely. SIADH secondary to malignancy in general, lymphoma in this case, was not fully excluded. Watabe and colleagues reported a case of IVL with SIADH, which was suggested to result from the infiltration of lymphoma cells into the pituitary gland; however, SIADH developed after two cycles of chemotherapy containing cyclophosphamide and vincristine (17). In the present case, the effect of cytotoxic agents on SIADH was denied, because chemotherapy was not administered at any course of the disease.

In summary, the present case, considered as a classical, non-Asian variant of IVL, interestingly showed that in some cases of IVL SIADH may progress before generalized symptoms and marked organomegaly develop.

References


