Expert Endocrine Consult

Suspected Primary Adrenal Lymphoma (PAL) Associated With Hemophagocytic Lymphohistiocytosis (HLH)

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Abbreviations: ACTH, adrenocorticotropic hormone; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; HLH, hemophagocytic lymphohistiocytosis; PAL, primary adrenal lymphoma; PCR, polymerase chain reaction.

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Abstract

Adrenal incidentalomas, masses noted on imaging performed for other purposes, are common, with 10% to 15% presenting as bilateral adrenal masses. These cases can be challenging as the differential diagnosis is broad, including metastatic disease, primary adrenal lymphoma (PAL), or infection, and often requiring a biopsy if initial biochemical workup is unrevealing. We present here a relevant case description, laboratory and radiologic imaging studies, and discussion of literature. A 62-year-old Korean woman presented with altered mental status and fevers. She was found to have bilateral adrenal incidentalomas and retained acupuncture needles. Adrenal workup did not show biochemical evidence of hormonal excess. Infectious workup was unrevealing, as was a metal/toxin workup due to retained acupuncture needles. Fevers and episodes of hypotension persisted which prevented the patient from obtaining an adrenal biopsy. Bone marrow biopsy was obtained for pancytopenia and revealed B-cell lymphoma with large cell morphology and few histiocytes with hemophagocytosis, raising concern for lymphoma-induced hemophagocytic lymphohistiocytosis (HLH). PAL associated with HLH was highly suspected in our patient, given the large (7 cm) bilateral adrenal masses and bone marrow biopsy findings of lymphoma. The patient was treated for diffuse large B-cell lymphoma, with clinical improvement. PAL is a rare but aggressive lymphoma
Adrenal masses are often found incidentally when computed tomography (CT) or magnetic resonance imaging (MRI) is done for other purposes. A recent study using high-resolution CT scans reported a prevalence of 5%, which is similar to that found in autopsy studies [1]. Prevalence estimates of adrenal incidentalomas increase with age, with a prevalence of 0.2% in those 20 to 29 years of age and up to 7% for those older than 70 years [2]. Bilateral masses are found in 10% to 15% of cases in an analysis of 2 large adrenal incidentaloma studies [3, 4]. The differential diagnosis for bilateral adrenal masses is broad and includes metastatic disease, infiltrative disease, lymphoma, infection (tuberculosis, fungal), hemorrhage, congenital adrenal hyperplasia, bilateral cortical adenomas, and primary bilateral macronodular adrenal hyperplasia. Definitive diagnosis can sometimes be difficult when initial hormonal and infectious workup are negative.

Case

A 62-year-old Korean woman with no significant past medical history presented with altered mental status and later developed persistent fevers. She was recently hospitalized for presumed viral encephalitis with symptoms of speech difficulties, memory deficits, visual hallucinations, and bilateral hand numbness. Her physical exam was unremarkable. CT scan of the abdomen with intravenous contrast revealed indeterminate bilateral adrenal enlargement measuring 80 Hounsfield units, right adrenal gland measuring 7.0 × 3.0 cm and left adrenal measuring 6.9 × 3.2 cm (Fig. 1). Also noted were retained acupuncture needles. Adrenal workup revealed elevated adrenocorticotropic hormone (ACTH) of 106 pg/mL [reference range, 7.2-63.3 pg/mL] but normal random total cortisol of 19.2 μg/dL [6.0-18.4 μg/dL] and normal late night/midnight salivary cortisol × 3 [<100 ng/dL]. Results showed a normal plasma metanephrine level of <10.0 pg/mL [0.0-88.0 pg/mL] and normal plasma normetanephrine 33.2 pg/mL [0.0-191.8 pg/mL]. Infectious workup was negative for urine histoplasma antigen, QuantiFERON-TB Gold (QFT), Lyme polymerase chain reaction (PCR), SARS-CoV-2 Virus (COVID-19), hepatitis B, Epstein-Barr virus (EBV), herpes simplex virus (HSV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV). Cerebrospinal fluid (CSF) studies from lumbar puncture showed a white blood cell count of 11/μL with lymphocytic predominance at 85% and elevated protein to 121 mg/dL. The CSF PCR panel was negative for common meningitis/encephalitis infections, including Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitides, Streptococcus agalactiae, Streptococcus pneumoniae, CMV, Enterovirus, HSV-1, HSV-2, Human herpesvirus 6, parechovirus, varicella, and cryptocooccus. A toxicology panel and metal toxicity screen for mercury, lead, cadmium, and arsenic were also negative (Table 1). She was treated initially with plasmapheresis for presumed autoimmune encephalitis while the CSF autoimmune panel was pending. Fevers developed after the fourth session of plasmapheresis and were persistent. Pancytopenia, hypotensive episodes, and worsening encephalopathy occurred despite the treatment (Fig. 2). Electroencephalography showed mild intermittent generalized slowing and findings consistent with mild multifocal cerebral dysfunction, while MRI and CT scan of the head showed no evidence of acute intracranial changes (Fig. 3).

The elevated ACTH of 106 pg/mL in the setting of a normal random cortisol was an interesting finding and we suspected acute physiologic illness, partial adrenal insufficiency/adrenal hypofunction, ectopic ACTH secretion, lab assay error, or adrenal hyperplasia as possible causes. Persistent hypotension and fevers prompted evaluation for adrenal insufficiency and a 250 μg cosynthropin stimulation test was performed. Baseline cortisol was 19.2 μg/dL.
followed by 17.5 μg/dL at 30 minutes and 18.3 μg/dL at 60 minutes post-stimulation. Cortisol at baseline and after cosyntropin stimulation were in the 18 to 20 μg/dL range, making adrenal insufficiency less likely. Multidisciplinary meeting between endocrine, neurology, and infectious disease clinicians also addressed the possibility of ectopic ACTH or a paraneoplastic syndrome to explain the patient’s clinical course. Infectious disease and neurology teams recommended prompt surgical removal of “tumors” in the context of the patient’s declining clinical course. However, based on the endocrine workup, which showed the masses to be non-hormone secreting, adrenal biopsy prior to any surgical intervention was advocated for.

Adrenal biopsy was recommended but deferred due to the patient’s hemodynamic instability. Bone marrow biopsy was scheduled due to suspected malignancy given pancytopenia and fever of unknown origin and revealed B-cell lymphoma with large cell morphology and few histiocytes with hemophagocytosis, raising concern for HLH (Fig. 4). PAL associated with HLH was highly suspected in our patient, given the large (7 cm) bilateral adrenal masses, bone marrow biopsy findings of lymphoma, and clinical symptoms of fever and mental status changes. The patient’s neurologic complications were attributed to her lymphoma as large B-cell lymphomas are known to involve any organ, with the skin and central nervous system (CNS) being the most affected. More than 60% of patients develop neurologic manifestations, including encephalopathy, seizure, myelopathy, neuropathy, and radiculopathy [5]. Additionally, there was no other lymph node involvement noted in CT pan-scan. The patient was started on rituximab and reduced-dose cyclophosphamide, doxorubicin, vincristine and prednisolone (R-mini-CHOP) for diffuse large B-cell lymphoma (DLBCL), given her bicytopenia of anemia and thrombocytopenia. The HLH-94 treatment protocol with etoposide 150mg/m² and dexamethasone 10mg/m² and intrathecal methotrexate and hydrocortisone for the CNS involvement was initiated. The patient’s mental status gradually improved and fevers subsided over the course of 3 weeks. She was discharged from the hospital with a plan for a repeat CT scan of the abdomen after her second or third cycle of chemotherapy to evaluate for the therapeutic effects of lymphoma treatment on the suspected PAL. Cycle 3 of chemotherapy with R-CHOP and intrathecal methotrexate was completed outpatient on September 8, 2020, and surveillance imaging with skull-to-thigh positron emission tomography–CT was obtained September 26, 2020. Results showed resolved bilateral adrenal thickening and no adrenal fluorodeoxyglucose avidity (Fig. 5). Importantly, the patient followed up with outpatient endocrine and reported no interval symptoms, resolution of fevers, and improvement in neurologic function.

Table 1. Laboratory Findings

| Laboratory Value      | Reference Range |
|-----------------------|-----------------|
| Blood cell count      | Admission 8 weeks 3.80-10.50 |
| White blood cell count, K/μL | 6.20 0.41 3.80-5.20 |
| Red blood cell count, M/μL | 3.89 2.63 11.5-15.5 |
| Hemoglobin, g/dL      | 12 7.1 34.5-45.0 |
| Hematocrit, %         | 36.5 22.0 150-400 |
| Platelet, K/μL        | 140 24 |
| Chemistry             |                 |
| Sodium, mmol/L        | 131 135-145     |
| Potassium, mmol/L     | 4.5 3.5-5.3     |
| Bicarbonate, mmol/L   | 27 22-31        |
| Calcium, mg/dL        | 9.1 8.4-10.5    |
| Serum creatinine, mg/dL | 0.64 0.5-1.30 |
| Lactate dehydrogenase, U/L | 806 50-242 |
| C-reactive protein, mg/dL | 2.26 0.00-0.40 |
| Creatinine kinase, U/L | <10 25-170 |
| Plasma normetanephrine, pg/mL | 33.2 0.0-191.8 |
| Plasma metanephrine, pg/mL | <10.0 0.0-88.0 |
| TSH, μU/mL            | 1.77 0.27-4.20 |
| Hemoglobin A1c, %     | 5.7 4.0-5.6     |
| ACTH baseline, pg/mL  | 106.0 7.2-63.3 |
| Cosyntropin stimulation test, 0.25 mg Cortisol, μg/dL | 6.0-18.4 |
| Baseline              | 19.2 |
| 30 minutes            | 17.5 |
| 60 minutes            | 18.3 |
| Midnight salivary cortisol, ng/dL | <50 <100 |
| CSF                   |                 |
| Total nucleated cell count, μL | 11 0-5 |
| Lymphocytes, %        | 85 40-80        |
| Protein, mg/dL        | 121 15-45       |
| Metal/toxin screen    |                 |
| Mercury, μg/L         | 3.7 0.0-14.9    |
| Lead, μg/dL           | None detected 0-4 |
| Cadmium, μg/L         | 0.7 0.0-1.2     |
| Arsenic, μg/L         | 7 2-23          |
| Infection panel       |                 |
| COVID-19, PCR         | Not detected    |
| Epstein-Barr virus, IU/mL | Not detected 49-1.69E+08 |
| HIV Ag/Ab combo       | Nonreactive Nonreactive |
| QuantiFERON-TB Plus Urine histoplasma antigen, ng/mL | Negative Negative 0.00-0.10 Negative |
Figure 2. Timeline representing the patient's significant hospital course and outpatient follow up.

Figure 3. Neurological evaluation. (A) Abnormal EEG which showed mild intermittent generalized slowing. Findings indicated mild multifocal cerebral dysfunction with no epileptiform activity. (B) Brain MRI with normal pituitary gland anatomy.
Discussion

We report a challenging case of a patient who presented with encephalopathy and fever of unknown origin. She was found to have bilateral adrenal mass suspicious for PAL from DLBCL. This case illustrates the diagnostic and management difficulties of bilateral adrenal masses in patients unable to receive adrenal biopsy and thus without tissue confirmation of diagnosis.

The incidence of secondary adrenal involvement detectable on CT scan in non-Hodgkin lymphoma is approximately 5% but that incidence rises to 25% to 35% when autopsy cases are included. PAL is rarer, accounting for less than 1% of cases of non-Hodgkin lymphoma [6]. The most common type of PAL is DLBCL, which accounts for more than 70% of cases [7]. There is currently no strict definition for PAL but it is widely accepted among experts to be histologically proven lymphoma that involves one or both adrenal glands with no prior history of lymphoma elsewhere and adrenal lesions that are dominant if other sites are involved.

A recent systematic review of case reports for PAL by Rashidi et al reveals that Asia is the most common continent of origin at 54%, compared with 21% in Europe and 20% in North America. B-symptoms (68%), pain (42%), and fatigue (36%) were the most common symptoms reported in the reported cases, followed by anorexia (23%), nausea and vomiting (14%), neurological symptoms (7%), and diarrhea (4%) [7]. Bilateral PAL cases were found to be present with B-symptoms more often than unilateral cases, 73% compared to 53%, respectively. The higher incidence of B-symptoms has been hypothesized to be a result of higher tumor burden causing cytokine storm.

Interestingly, adrenal insufficiency was present in 61% of PAL cases, which is unexpectedly common, given the fact that most of the adrenal cortex needs to be destroyed before hypofunction becomes apparent [8]. Infiltration of the adrenal gland by other metastatic diseases is common; autopsy reports indicate that adrenal metastasis is present in 40% to 60% of patients with disseminated lung or breast cancer, 30% of patients with melanoma, and 14% to 20% of patients with stomach or colon cancer [9, 10]. Despite the high incidence of metastatic diseases to the adrenal glands, previous studies found clinical adrenal insufficiency in only 19% to 33% of patients with metastatic disease to the adrenal glands [11, 12]. Though the exact mechanism of the significantly higher incidence of adrenal insufficiency in PAL compared with other malignancies remains to be elucidated, it is postulated to be due to cytokine-driven changes in the adrenal microenvironment by the PAL.

HLH associated with PAL has been described in a handful of case reports in the literature [13-15]. It is a life-threatening syndrome caused by excessive inflammation and tissue destruction due to abnormal immune activation. In HLH, macrophages are excessively activated and secrete cytokines that can lead to severe cellular damage. The natural killer cells and cytotoxic lymphocytes that normally eliminate activated macrophages are also impaired. It is known to develop in patients with malignancies, mainly lymphoid cancers and leukemia, but it can
also occur in patients with solid tumors. Diagnosis should be prompt, since the survival is approximately 2 months without treatment in patients diagnosed with HLH [16]. The mainstay of treatment is the HLH-94 protocol with etoposide and dexamethasone given at tapering doses over 8 weeks, with the addition of intrathecal methotrexate and hydrocortisone for those with CNS involvement. Overall the prognosis is still poor on HLH-94 protocol, the median survival is 54% at 6.2 years, and those with neurological involvement had lower survival at 40% compared to those without at 67% [17].

Adrenal DLBCL has a worse prognosis compared to other DLBCL, with a median survival time of only 14 months in a recent cohort study. B-symptoms, bone marrow involvement, and lymphoma grade were not found to be associated with survival differences. Renal insufficiency, age greater than 70 years, bilateral involvement, and adrenal insufficiency were identified as poor prognostic factors. The authors also found chemotherapy to be associated with significant survival benefits [18].

Treatment of PAL is similar to treatment of other types of DLBCL. Kim et al reported 2-year overall and progression-free survival rates of 68% and 51%, respectively on R-CHOP chemotherapy in their retrospective multicenter study. Complete remission was achieved in 55% of patients and it was a significant predictor of longer overall and progression-free survival [19]. The retrospective study included 7 patients who received adrenalectomy before R-CHOP and it was not associated with survival benefits. Based on this finding, it may be beneficial to preserve as much normal adrenal tissue as possible to maintain adrenal function, as adrenal insufficiency is a negative prognostic factor.

PAL is a rare but aggressive lymphoma with few reported cases. It should be part of the differential for both unilateral and bilateral adrenal masses. An early diagnosis is crucial as the main treatment is chemotherapy rather than surgery and it confers a significant survival benefit. A biopsy of the adrenal mass should be performed, when possible, after the biochemical exclusion of pheochromocytoma if PAL is suspected.

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