Primary adrenal lymphoma with adrenal insufficiency: report of three cases and review of literature

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Conflict of Interest: none
Primary adrenal lymphoma (PAL) is an extremely rare disease with a high incidence of bilateral adrenal involvement whose prognosis is usually poor even with aggressive chemotherapy such as (R)-CHOP.

Here we report three patients with PAL. All of them initially presented with adrenal insufficiency, which later turned out to be due to destruction of both adrenal cortices by diffuse large B-cell lymphoma (DLBCL).
Case 1
A 69-year-old man
Chief Complaint

- Lack of appetite
- Weight loss (4 kg / 1 month)
- Slight low back pain

History of Present illness

1 month before admission
- His chief complaint started.

2 days before admission
- Plain CT scan detected bilateral adrenal mass lesions.
- He was referred to our hospital.
Physical Examination

Blood pressure: 102/64 mmHg
Pulse rate: 85 /min
Temperature 36.0 °C

Consciousness: alert
Skin: No pigmentation,
    No enlarged lymph nodes
HEENT: unremarkable
Heart /Lung/Abdomen: unremarkable
Extremities: unremarkable
### Laboratory Data on Admission
(After administration of Dexamethasone 6.6mg)

<table>
<thead>
<tr>
<th>Blood Cell Count</th>
<th>Endocrinology</th>
<th>Immunology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb 12 g/dl</td>
<td>ALP 240 U/l</td>
<td>sIL-2R 7404 U/ml</td>
</tr>
<tr>
<td>WBC 3300/ul</td>
<td>γ-GTP 24 U/l</td>
<td>TK 36 U/l</td>
</tr>
<tr>
<td>Neu 82%</td>
<td>CK 40 U/l</td>
<td>EB-VCA-IgG 1:80</td>
</tr>
<tr>
<td>Lym 17%</td>
<td>BUN 15.5 mg/dl</td>
<td>EB-VCA-IgM &lt;1:10</td>
</tr>
<tr>
<td>Other 1%</td>
<td>Cr 0.86 mg/dl</td>
<td>EBNA 1:40</td>
</tr>
<tr>
<td>Plt 24x10⁴/ul</td>
<td>Na 125 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Hct 36.1%</td>
<td>K 4.8 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td>Cl 89 mEq/l</td>
<td></td>
</tr>
<tr>
<td>TP 7.2 g/dl</td>
<td>Glu 152 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Alb 4.1 g/dl</td>
<td>HbA1c 5.3%</td>
<td></td>
</tr>
<tr>
<td>T-bil 0.68 mg/dl</td>
<td>CRP 6.2 mg/dl</td>
<td></td>
</tr>
<tr>
<td>AST 48 U/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT 29 U/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH 810 U/l</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Urinary-Biochemistry
- U-VMA 1.6 mg/l

### Cosyntropin stimulation test

<table>
<thead>
<tr>
<th>Cortisol (µg/dL)</th>
<th>Baseline</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

| PAC (pg/mL)      | 45.8     | 20.8   | 29.7   |

**TK:** Thymidine Kinase  
**EB-VCA-IgG:** Epstein-Barr Virus IgG Antibody to Viral Capsid Antigen  
**EB-VCA-IgM:** Epstein-Barr Virus IgM Antibody to Viral Capsid Antigen  
**EBNA:** Epstein-Barr Virus Nuclear Antigen
Figure 1. A: Contrast-enhanced CT showed large, irregular, heterogeneous adrenal masses. B: PET-CT fusion image showed intense FDG uptake in bilateral adrenal masses. (SUV-max, early phase 22.44; delayed phase 23.99)
Pathological Findings

Figure 1. C: Hematoxylin-Eosin (H-E) staining. Immunohistochemical staining demonstrated that both CD20 was positive. Ki-67 labeling Index is 80-90%.
# Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R-CHOP</strong></td>
<td>Rituximab 375 mg/m² (day1)+Cyclophosphamide 750 mg/m² (day1)+adriamycin 50 mg/m² (day1)+Vincristine 1.4 mg/m² (day1)+Prednisone 60 mg/body (day1-5)</td>
</tr>
<tr>
<td><strong>ESHAP</strong></td>
<td>Etoposide 40 mg/m² (day1-4)+Methylprednisolone 500 mg/body (day1-5)+Cytarabine 2000 mg/m² (day5)+Cisplatin 25 mg/m² (day1-4)</td>
</tr>
<tr>
<td><strong>GCD</strong></td>
<td>Gemcitabine 1000 mg/m² (day1,8) +Carboplatin 5 AUC(day1)+Dexamethasone 33 mg/body (day1-4)</td>
</tr>
<tr>
<td><strong>SMIL</strong></td>
<td>Dexamethasone 40 mg/body (day2-4)+Methotrexate 2000 mg/m² (day1)+Ifosfamide 1500 mg/m² (day2-4)+L-asparaginase 6000 U/m² (day8,10,12,14,16,18,20)+Etoposide 100 mg/m² (day2-4)</td>
</tr>
<tr>
<td><strong>R-</strong></td>
<td>Rituximab 375 mg/m² (day1)</td>
</tr>
</tbody>
</table>
Case 2
A 68-year-old man
Chief Complaint

- Anorexia
- Weight loss (5 kg/2 month)
- Low back pain
- Pigmentation

History of Present illness

2 months before admission
- Anorexia, Weight loss, and Pigmentation

1 month before admission
- Low back pain
Physical Examination

Blood pressure: 122/70 mmHg
Pulse rate 66 /min
Temperature 36.1 °C

Consciousness: alert
Skin: Pigmentation of face, oral mucosa and elbows. Anterior cervical lymph nodes were enlarged.
HEENT: unremarkable
Heart /Lung/Abdomen: unremarkable
Extremities: unremarkable
## Laboratory Data on Admission

### Blood Cell Count
- **Hb**: 14.4 g/dl
- **WBC**: 4600 /ul
- **Neu**: 48%
- **Lym**: 36%
- **Other**: 16%
- **Plt**: 20x10⁴ /ul
- **Hct**: 40.4%

### Biochemistry
- **TP**: 7.9 g/dl
- **Alb**: 4.0 g/dl
- **T-bil**: 0.80 mg/dl
- **AST**: 33 U/l
- **ALT**: 21 U/l
- **LDH**: 307 U/l
- **ALP**: 273 U/l
- **γ-GTP**: 86 U/l
- **CK**: 50 U/l
- **BUN**: 8.7 mg/dl
- **Cr**: 0.66 mg/dl
- **UA**: 3.0 mg/dl
- **Na**: 128 mEq/l
- **K**: 4.3 mEq/l
- **Cl**: 94 mEq/l
- **Glu**: 97 mg/dl
- **HbA1c**: 5.3%
- **CRP**: 4.0 mg/dl

### Endocrinology
- **DHEA-S**: 102 ng/ml
- **ACTH**: 262 pg/ml
- **Cortisol**: 6.6 µg/dl
- **PRA**: 2.0 ng/ml/hr
- **PAC**: 51 pg/ml
- **SIL-2R**: 1074 U/ml

### Immunology
- **QF-T**: (-)

### Urinary-Biochemistry
- **U-MN**: 0.01 mg/l
- **U-NMN**: 0.45 mg/l
- **U-Cr**: 59.9 mg/dl

### Cosyntropin stimulation test

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortisol (µg/dL)</strong></td>
<td>3.5</td>
<td>3.1</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>PAC (pg/mL)</strong></td>
<td>39.2</td>
<td>26.0</td>
<td>36.1</td>
</tr>
</tbody>
</table>

QF-T: QuantiFERON-TB Gold
Figure 2. A: Contrast-enhanced CT showed slightly enhanced and homogeneous bilateral adrenal masses. B: PET-CT fusion image showed intense FDG uptake in bilateral adrenal masses. (SUV-max, early phase 26.63; delayed phase 34.60)
Pathological Findings

Figure 2. C: Cut gross specimens of the left adrenal tumor.
Figure 2. D: Histological study of the adrenal tumor. Hematoxylin-Eosin (H-E) staining. Immunohistochemical staining demonstrated that both CD20 and CD79a were positive. Ki-67 labeling Index is 90%.
Clinical Course

- **R-CHOP**
- **Radiation 50Gy**
- **R-ESHAP**
- **R-DeVIC**
- **R-GDP**

**sIL-2R** (U/ml)

**LDH** (U/l)

Weeks: 0, 10, 20, 30, 40, 50, 60, 70, 80
## Chemotherapy Regimen

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<tbody>
<tr>
<td>R-CHOP</td>
<td>Rituximab 375 mg/m² (day 1) + Cyclophosphamide 750 mg/m² (day 1) + Adriamycin 50 mg/m² (day 1) + Vincristine 1.4 mg/m² (day 1) + Prednisone 60 mg/body (day 1-5)</td>
</tr>
<tr>
<td>DeVIC</td>
<td>Dexamethasone 40 mg/body (day 1-3) + Etoposide 100 mg/m² (day 1-3) + Ifosfamide 1500 mg/m² (day 1-3) + Carboplatin 300 mg/m² (day 1)</td>
</tr>
<tr>
<td>GDP</td>
<td>Gemcitabine 1000 mg/m² (day 1, 8) + Dexamethasone 40 mg/body (day 1-4) + Cisplatin 75 mg/m² (day 1)</td>
</tr>
<tr>
<td>R-</td>
<td>Rituximab 375 mg/m² (day 1)</td>
</tr>
</tbody>
</table>
Case 3
A 63-year-old man
Chief Complaint

- Anorexia
- Weight loss (4 kg / 4 months)
- High fever
- Nocturnal sweating

History of Present illness

4 months before admission
- Anorexia and weight loss

3 weeks before admission
- Low back pain
Physical Examination

Blood pressure: 98/64 mmHg
Pulse rate: 108 /min
Temperature: 38.9 °C

Consciousness: alert
Skin: No pigmentation,
   No enlarged lymph nodes
HEENT : Conjunctiva palpebrae: anemic
Heart /Lung/Abdomen: unremarkable
Extremities : unremarkable
### Laboratory Data on Admission

#### Blood Cell Count
- **Hb**: 9.6 g/dl
- **WBC**: 10400/ul
- **Neu**: 72%
- **Lym**: 4%
- **Other**: 24%
- **Plt**: 14x10⁴/ul
- **Hct**: 29.8 g/dl

#### Biochemistry
- **TP**: 5.8 g/dl
- **Alb**: 2.2 g/dl
- **T-bil**: 0.49 mg/dl
- **AST**: 23 U/l
- **ALT**: 15 U/l
- **LDH**: 236 U/l
- **γ-GTP**: 16 U/l
- **CK**: 8 U/l
- **BUN**: 8.3 mg/dl
- **Cr**: 0.76 mg/dl
- **UA**: 3.9 mg/dl
- **Na**: 131 mEq/l
- **K**: 4.3 mEq/l
- **Cl**: 98 mEq/l
- **Glu**: 97 mg/dl
- **HbA1c**: 4.9%
- **LDH**: 236 U/l
- **HbA1c**: 4.9%

#### Endocrinology
- **DHEA-S**: 295 ng/ml
- **ACTH**: 87 pg/ml
- **Cortisol**: 14.6 µg/dl
- **PRA**: 2.1 ng/ml/hr
- **PAC**: 129 pg/ml

#### Immunology
- **sIL-2R**: 18936 U/ml
- **TK**: 32.5 U/l
- **EB-VCAG**: 1:160
- **EB-VCAM**: <1:10
- **EBNA**: 1:40
- **QF-T**: (-)

#### Urinary-Biochemistry
- **U-MN**: 0.05 mg/day
- **U-NMN**: 0.46 mg/day
- **U-Cor**: 121 µg/day

#### Cosyntropin stimulation test

<table>
<thead>
<tr>
<th>Time</th>
<th>Cortisol (µg/dL)</th>
<th>PAC (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14.6</td>
<td>129</td>
</tr>
<tr>
<td>30 min</td>
<td>15.5</td>
<td>159</td>
</tr>
<tr>
<td>60 min</td>
<td>17.4</td>
<td>185</td>
</tr>
</tbody>
</table>

**Note:**
- **TK**: Thymidine Kinase
- **QF-T**: QuantiFERON-TB Gold
- **EB-VCA-IgG**: Epstein-Barr Virus IgG Antibody to Viral Capsid Antigen
- **EB-VCA-IgM**: Epstein-Barr Virus IgM Antibody to Viral Capsid Antigen
- **EBNA**: Epstein-Barr Virus Nuclear Antigen
Figure 3. A: Plain CT scan showed bilateral adrenal masses.
Figure 3. B: FDG PET-CT fusion image showed intense FDG uptake in bilateral adrenal masses, stomach wall, cardiac lymph node, lower thoracic paraesophageal lymph nodes, lymph nodes along the superior mesenteric artery, and para-aortic lymph node. (SUV-max, early phase 21.29)
Endoscopic findings

Figure 3. C: Endoscopic findings of gastric body showed multiple submucosal elevated lesions with ulcer.
Figure 3. D: Histological study of the adrenal tumor. Hematoxylin-Eosin (H-E) staining. Immunohistochemical staining demonstrated that both CD20 and CD5 were positive. Ki-67 labeling Index is 80%.
Clinical Course

- Day1: LDH ~18936 (U/ml)
- Day51: SIL-2R ~14651 (U/ml)
- Day101: LDH
- Day151: LDH
- Day201: LDH
- Day251: LDH

Treatment: R-CHOP
# Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose and Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R-CHOP</strong></td>
<td>Rituximab 375 mg/m² (day 1) + Cyclophosphamide 750 mg/m² (day 1) + Adriamycin 50 mg/m² (day 1) + Vincristine 1.4 mg/m² (day 1) + Prednisone 60 mg/m² (day 1-5)</td>
</tr>
</tbody>
</table>
Figure 3. E: After six cycles of R-CHOP therapy. Plain CT scan showed shrinkage of bilateral adrenal masses. (Partial Response)
Discussion
Definition

Primary adrenal lymphoma

A histologically proven lymphoma that involves one or both adrenal glands.

- At presentation, no prior history of lymphoma elsewhere.

- Unequivocally dominant adrenal lesions, in cases with lymph nodes or other organ involvement.

Epidemiology

- Extremely rare disease < 200 cases reported (Asia 54%, Europe 21%, North America 20%)
- The mean age at diagnosis = 62 years old
- Male : Female = 1.8 : 1

Histology

- DLBCL 75%
- Peripheral T-cell lymphoma 7%
- Extranodal NK/T cell lymphoma 2%

(Ann Hematol 2013;92:1583)
Initial signs and symptoms

- Worsening of general state
- Weight loss
- Anorexia
- Abdominal pain
- Fever
- Digestive disorder
- Back pain
- Neurological symptoms
- Sweat
- Incidentaloma

Adrenal insufficiency

50-70% of bilateral PAL patients ⇨ Primary adrenal insufficiency (PAI).

Symptoms
- Fatigue, Anorexia, Weight loss, Skin pigmentation

Laboratory findings
- Low baseline serum cortisol level
- Inadequate response to Cosyntropin stimulation test

(Ann Hematol 2013;92:1583)
Adrenal insufficiency

50-70% of bilateral PAL patients
⇒ Primary adrenal insufficiency (PAI).

Etiology

- Direct infiltration by neoplastic lymphoid cells
- Autoimmune adrenalitis (Hypothesis)

(No correlation between the size of tumor and the extent of adrenal dysfunction (-Dutta et al))

(Turk J Gastroenterol 2015; 26: 85)
(Clin Med J 2009;122: 2616)
(Ann Hematol 2013; 92: 1583)
(Endocrinologist 2005; 15: 340)
### Prognosis

<table>
<thead>
<tr>
<th></th>
<th>A. Rashidi et al</th>
<th>C. Laurent et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year overall survival rates</td>
<td>68%</td>
<td>61.1%</td>
</tr>
<tr>
<td>2-year progression-free survival rates</td>
<td>51%</td>
<td>49.9%</td>
</tr>
<tr>
<td>Complete remission</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>32%</td>
<td></td>
</tr>
</tbody>
</table>

## Our cases

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Sex</td>
<td>69 /man</td>
<td>68 /man</td>
<td>63 /man</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Japanese</td>
<td>Japanese</td>
<td>Japanese</td>
</tr>
<tr>
<td>Adrenal Insufficiency</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>IV / High risk</td>
<td>IV / High risk</td>
<td>IV / High risk</td>
</tr>
<tr>
<td>Pathology</td>
<td>DLBCL</td>
<td>DLBCL</td>
<td>DLBCL</td>
</tr>
<tr>
<td>Therapy</td>
<td>Chemotherapy + Radiotherapy</td>
<td>Chemotherapy + Radiotherapy + Surgery</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Dead, after 350 days</td>
<td>Dead, after 567 days</td>
<td>Alive 352 days</td>
</tr>
</tbody>
</table>
Take home message

■ PAL should be considered as a possible cause of bilateral adrenal masses.

■ Approximately 50-70% of bilateral PAL patients develop adrenal insufficiency, which in itself can be life-threatening if untreated.

Therefore, adrenocortical function should be promptly evaluated.
Take home message

- Glucocorticoid replacement therapy should be started immediately, but carefully especially at high dose, because it can theoretically interfere with histopathological evaluation.
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1 Department of Internal Medicine, Teikyo University School of Medicine
2 Department of Pathology, Teikyo University Hospital
3 Department of Pathology, Teikyo University School of Medicine

Conflict of Interest: none