Lymphocytic Adrenal Medullitis: Case Report of A Patient with Pheochromocytoma-Like Hypertensive Paroxysms

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Key words
Adrenal, medullitis, inflammation, hypertension

ABSTRACT
Lymphocytic adrenal medullitis (LAM) denote the histological finding of lymphocytic infiltrates in the adrenal medulla, a rare phenomenon that previously has been deemed asymptomatic and linked to autopsy findings in patients with type I diabetes. We describe the finding of LAM in a 66-year old female presenting with hyperaldosteronism and a 17 mm lesion in the right adrenal gland. The patient displayed secondary hypertension as well as intermittently occurring exaggerated hypertensive episodes with systolic peaks above 220 mm Hg. Preoperative catecholamine screening was negative, diminishing the possibility of a pheochromocytoma. Unilateral adrenalectomy was performed, and histology revealed an aldosterone producing adrenocortical adenoma. No signs of adrenomedullary hyperplasia or pheochromocytoma were found; however, prominent B- and T-lymphocytic infiltrates were observed across the medulla. The inflammation was almost absent in the surrounding adrenocortical tissue. Postoperatively, the patient remained hypertensive, but without paroxysmal excessive blood pressure elevations. A review of our pathology records between the years 2000 to present time as well as focused histopathological re-examination of 40 cases revealed no signs of LAM in any adrenal gland investigated, confirming the occurrence in living patients as exceedingly rare. This is the first report of LAM in a living patient, with a possible clinical association to intermittent episodes of markedly increased blood pressure not commonly seen in patients with hyperaldosteronism. A coupling between LAM and exaggerated hypertensive episodes cannot be ruled out.

Case Presentation
The patient is a 66-year old female of Caucasian ethnicity with no family history of adrenal disease. She underwent splenectomy in 2005 due to immune thrombocytopenic purpura (ITP) and was admitted to a local hospital in 2009 because of nautical vertigo and hypertension (220/120 mmHg). At this point, potassium was normal and she was treated with 10 mg enalapril and 10 mg felodipin. Blood test showed ordinary aldosterone (376 pmol/L) and a low renin (1.2 ng/L), giving an ARR quotient of 313, see Table 1. U-cortisol was slightly elevated, but there were no signs of Cushing’s syndrome. Urine sample of catecholamine was normal. Blood pressure normalized (135/75 mm Hg) upon treatment. She was also treated with simvastatin since her cholesterol levels were elevated. During the years, her blood pressure was reasonably stable with an addition of 25 mg metoprolol in 2010.

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Bibliography
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In the fall of 2016, the patient presented with increased and fluctuating blood pressure and later also hypokalaemia, ranging from 3.0–3.3 nmol/L. She was once again admitted at another local hospital because of chest pain, tiredness and occasional hypertensive episodes. Her blood pressure could within 3 h change from 140/95 to 270/135. During a three-day stay, paroxysmic elevations in blood pressure were observed. 750 mg of kaleorid normalized potassium levels in doses 5 + 5 daily. An increased ARR quotient was once again found. P-metoxynoradrenaline and p-metoxyadrenaline was analyzed twice; both normal, as was P-adrenaline and P-noradrenaline. A subsequent CT scan demonstrated a 17 × 13 × 10 mm large mass in the right adrenal with Houndsfield units - 3. Her medication was changed to losartan 100 mg, amlodipin 10 mg and doxacozin 4 mg twice daily, which normalized blood pressure (144/62 to 110/60 mmHg). Catheterization of the adrenal veins lateralized to the right. Laparoscopic adrenalectomy was performed at the Karolinska University Hospital to where she was referred. Postoperatively, blood pressure was regulated with 25 mg of metoprolol and 5 mg amlodipine, and her rapid fluctuations in blood pressure vanished after surgery.

**Histopathology**

The right adrenal gland weighted 13,2 grams and measured 5 × 4 × 1.5 cm. A single 1.5 × 1.5 × 1.2 cm lesion with a yellowish cut surface was observed expanding the adrenocortex, no further lesions were observed. In addition, the adrenal medulla was focally observed with a white-yellowish cut surface, which is not normally seen when grossing the adrenal gland. Routine histopathology verified the 1.5 cm lesion as an adrenocortical adenoma composed of a circumscribed lipid-rich cells with a low nuclear-to-cytoplasmic ratio (▶ Fig. 1a). A Weiss score, an established way of determining malignant potential in adrenocortical lesions, yielded zero points, thereby ruling out this lesion as malignant. The lesion was uniformly positive for CYP11B2 (aldosterone synthase) and negative for CYP11B1 (responsible for conversion of progesterone to cortisol) immunoreactivity, verifying the lesion as aldosterone producing (▶ Fig. 1b). The surrounding adrenocortex showed no nodular expansions, thereby excluding micronodular hyperplasia. Moreover, the surrounding tissue showed microscopic cell clusters with intense CYP11B2 immunoreactivity denoted “aldosterone producing cell clusters” (APCC) which are regularly observed in a large subset of non-tumorous adrenals. The clinical significance of APCC is unknown, but recent molecular studies suggest that APCC might be a precursor of aldosterone producing adenomas [1].

The adrenal medulla was focally seen with a slight increase in width (3 mm), but with no nodular expansions suggestive for adrenomedullary hyperplasia. Moreover, the adrenal medulla was observed with small nodules of mature lymphocytes, but without medullar atrophy or fibrosis (▶ Fig. 2a). Immunohistochemical investigations confirmed the nodules as lymphocytic (CD45 + ), with a predominance of type B-lymphocytes (CD20 + ) admixed with T Helper (CD4 + ) and T Killer (CD8 + )-lymphocytes (▶ Fig. 2b). Extensive review of our pathology records revealed no signs of LAM in any adrenal gland (n = 704) investigated between the years 2000 to present time, confirming the occurrence of LAM as exceedingly rare in our patient material. To avoid reporting bias, we also reviewed a total of 40 adrenal glands exhibiting non-medullary conditions, for eventual LAM involvement. The cohort’s consisted of 21 aldosterone-producing adrenocortical adenomas, 14 adrenocortical hyperplasias (10 aldosterone-producing, 2 cortisol-producing and one with both aldosterone and cortisol production), 2 cortisol-producing adrenocortical adenomas, one non-producing adrenocortical adenoma, one adrenal with metastasing rectal adenosarcoma and one normal adrenal adjacent to an abdominal paraganglioma. For all these cases, the adrenal medulla was histo-

**Table 1** Laboratory measures at investigations during 2009 and 2016, and at post-operative follow-up 2017.

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2016</th>
<th>2016</th>
<th>2017</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>3.8</td>
<td>3.0</td>
<td>3.9</td>
<td>4.1</td>
<td>3.5–4.4 nmol/L</td>
</tr>
<tr>
<td>P-aldosterone</td>
<td>376</td>
<td>474</td>
<td>119</td>
<td>190–830 pmol/L (standing)</td>
<td></td>
</tr>
<tr>
<td>P-renin</td>
<td>1.2</td>
<td>1.2</td>
<td>16</td>
<td>3–33 ng/L (standing)</td>
<td></td>
</tr>
<tr>
<td>U-aldosterone</td>
<td>35</td>
<td>35</td>
<td></td>
<td></td>
<td>3.3–78 nmol/24 h</td>
</tr>
<tr>
<td>ARR</td>
<td>313</td>
<td>395</td>
<td></td>
<td></td>
<td>&gt; 100 suspect PA</td>
</tr>
<tr>
<td>U-adrenaline</td>
<td>36</td>
<td></td>
<td></td>
<td>2–80 nmol/24</td>
<td></td>
</tr>
<tr>
<td>U-noradrenaline</td>
<td>313</td>
<td></td>
<td></td>
<td>60–400 nmol/24 h</td>
<td></td>
</tr>
<tr>
<td>FP-metoxynoradrenaline</td>
<td>&lt;0.2</td>
<td>&lt;0.2</td>
<td></td>
<td></td>
<td>&lt;0.3 nmol/L</td>
</tr>
<tr>
<td>FP-metoxynorepinephrine</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
<td></td>
<td>&lt;1.1 nmol/L</td>
</tr>
<tr>
<td>P-adrenaline</td>
<td>&lt;0.3</td>
<td></td>
<td></td>
<td>0.7 nmol/L</td>
<td></td>
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<tr>
<td>P-noradrenaline</td>
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<td></td>
<td></td>
<td>1.6–4.8 nmol/L (standing)</td>
<td></td>
</tr>
<tr>
<td>U-ShIA</td>
<td>26</td>
<td>15</td>
<td></td>
<td>10–80 umol/L</td>
<td></td>
</tr>
<tr>
<td>Chromogranin A</td>
<td>2.3</td>
<td></td>
<td></td>
<td>&lt;3 nmol/L</td>
<td></td>
</tr>
<tr>
<td>U-cortisol</td>
<td>871</td>
<td></td>
<td></td>
<td>153–790 nmol/24 h</td>
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<tr>
<td>S-cortisol</td>
<td>593</td>
<td></td>
<td></td>
<td>240–730 mol/L</td>
<td></td>
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<tr>
<td>S-cortisol after dexamethason</td>
<td>31</td>
<td></td>
<td></td>
<td>&lt;50 nmol/L</td>
<td></td>
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<tr>
<td>P-ACTH</td>
<td>4.9</td>
<td></td>
<td></td>
<td>2–10 pmol/L</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1  a Photomicrographs of a hematoxylin-eosin stained adrenocortical adenoma at x40 and x100 magnifications without vascular or capsular invasion and devoid of prominent inflammation. b CYP11B2 (aldosterone synthase) immunohistochemistry of the adrenocortical adenoma at x40 and x100 magnifications displaying strong and diffuse cytoplasmic immunoreactivity in the majority of tumor cells, while the surrounding capsule and blood vessels stained negative as internal negative controls.

Fig. 2  a Photomicrograph of hematoxylin-eosin stained adreno-cortex (AC) and adrenal medulla (AM) at x40 magnification, with dense lymphocytic infiltrates (arrows) specifically confined to the latter compartment consistent with adrenal medullitis. Insert is magnified x400. b Immunohistochemical stainings for the common lymphocytic marker CD45 (large image), as well as CD4 (T helper cells), CD8 (T killer cells) and CD20 (B cells) at x40 magnification.
To our knowledge, this is the first report of LAM in human tissue not acquired from autopsy material, thereby excluding the possibility of post mortem lymphocytic infiltration. Moreover, this is the first case of LAM with a possible association to the clinical presentation. We speculate that the adrenomedullary inflammation perturbed the chromaffin cells and caused intermittent increases in plasma catecholamine levels, much like the hyperthyroid period seen in the initial phases of a giant cell thyroiditis associated with follicular cell lysis. However, as we did not observe an increase in plasma catecholamines and no standard collection of urine was performed, the assumed coupling between the finding of LAM and the patient’s symptomatology remain speculative. Interestingly, the patient is still hypertensive, albeit without the paroxysmal attacks of sudden rise in blood pressure. However, cure of hypertension after adrenalectomy is only noted in two thirds of patients and correlates positively with duration of disease and with the age of the patient [10]. Interestingly, the observed finding of APCC could potentially indicate a predisposition to develop aldosterone-producing lesions also in the contralateral adrenal gland; however the patient is currently displaying normal aldosterone-to-renin ratios, which argue against this theory.

In summary, we report the first case of LAM in a living patient with known autoimmune disease and intermittent sharp increases in systolic blood pressure.

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Conflict of Interest

The author reports no conflicts of interest in this work.

References


