Adrenocortical Carcinoma, Myxoid Variant
- A Case Report -

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Myxoid variant of adrenal cortical carcinoma is extremely rare and there have been only 16 such cases reported in the medical literature. Here we report on a case of 43-year-old woman with a left adrenal mass that was detected during the evaluation for Cushing’s syndrome. Left adrenalectomy was performed and the tumor weighed 347 g. The cut surface was predominantly myxoid and gelatinous with central hemorrhage and necrosis. Histologically, the tumor cells were rather small, uniform and polygonal with mild pleomorphism. It showed diverse morphologic patterns according to the amount of the myxoid stromal component. Making the diagnosis was not easy because the tumor was without areas of conventional adrenocortical carcinoma. Immunohistochemically, the tumor cells were positive for α-inhibin, synaptophysin and vimentin, but the tumor cells were negative for pan-cytokeratin and CAM 5.2. The immunophenotypes were identical to those of conventional adrenal cortical neoplasms. During the evaluation of a cytokeratin-negative and vimentin-positive retroperitoneal neoplasm with a myxoid component, the possibility of adrenal cortical tumor should be considered in spite that this is a very rare entity.

Key Words: Adrenocortical carcinoma; Myxoid; Cushing syndrome

CASE REPORT

A 43-year-old woman was referred to the National Cancer Center due to a left adrenal mass. She had been treated for hypertension, which was detected six months ago. She also complained of easy fatigue and thinning of the upper and lower extremities. During the evaluation under the clinical diagnosis of Cushing’s syndrome, diabetes mellitus and the left adrenal mass were found. Her height and weight were 159 cm and 63 kg, respectively. The blood pressure was 103/64 mmHg at the time of admission. The serum cortisol level, the 24 h urine cortisol and serum aldosterone level were 25.3 μg/dL (normal range: 4.3-22.4 μg/dL), 641.4 μg/dL (normal range: 28.5-213.7 μg/dL) and 32.9 ng/mL (normal range: 1-31 ng/dL) respectively. DHEA-S (Dihydroepiandrosterone), 17-ketosteroid, epinephrine, norepinephrine, vanillylmandelic acid (VMA) and metanephrine were all within the normal limits. Adrenocorticotropic hormone was suppressed (1.8 pg/mL, normal range: AM: 10-60 pg/mL, PM: 6-30 pg/mL). The electrolytes, including Na+, Cl- and...
K+, were in their normal ranges. Abdominal computerized tomography revealed a large, centrally necrotic solid mass in the left adrenal gland (Fig. 1A). No metastatic lesions were identified on the positron emission tomography scan. At operation, the tumor in the adrenal gland was adhered to adjacent organs such as the kidney and pancreas. The left kidney was separated by careful dissection, but the pancreatic adhesion was so tight that distal pancreatectomy, including removing the spleen and left adrenalectomy, were performed. After the excision, the serum cortisol level was normalized (5.4 μg/dL). Five months later,

Table 1. Reviews of adrenocortical carcinoma with myxoid component

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Size/weight</th>
<th>Endocrinologic abnormality</th>
<th>Mitosis</th>
<th>Vascular/capsular invasion</th>
<th>Metastasis</th>
<th>Last follow up status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41/F</td>
<td>9 cm/unknown</td>
<td>PA, PH</td>
<td>None</td>
<td>+/-</td>
<td>Unknown</td>
<td>Pleura Alive</td>
</tr>
<tr>
<td>2</td>
<td>45/M</td>
<td>17.5 cm/900 g</td>
<td>CS</td>
<td>1-4/50HPF</td>
<td>+/-</td>
<td>+</td>
<td>Dead</td>
</tr>
<tr>
<td>3</td>
<td>44/F</td>
<td>9 cm/180 g</td>
<td>Free cortisol ↑</td>
<td>4/10HPF</td>
<td>-/</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>48/M</td>
<td>7.7 cm/151.9 g</td>
<td>Conn syndrome</td>
<td>7/10HPF</td>
<td>+/-</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>43/F</td>
<td>6 cm/65 g</td>
<td>CS</td>
<td>6/10HPF</td>
<td>+/-</td>
<td>Liver</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>48/M</td>
<td>9 cm/195 g</td>
<td>CS</td>
<td>5/10HPF</td>
<td>+/-</td>
<td>Omentum</td>
<td>Dead</td>
</tr>
<tr>
<td>7</td>
<td>53/F</td>
<td>8.4 cm/138 g</td>
<td>CS</td>
<td>13/10HPF</td>
<td>+/-</td>
<td>Liver</td>
<td>Dead</td>
</tr>
<tr>
<td>8</td>
<td>51/M</td>
<td>16 cm/700 g</td>
<td>CS</td>
<td>5/10HPF</td>
<td>+/-</td>
<td>Liver, lung</td>
<td>Dead</td>
</tr>
<tr>
<td>9</td>
<td>63/F</td>
<td>11 cm/unknown</td>
<td>CS Aldosterone ↑</td>
<td>9/10HPF</td>
<td>+/-</td>
<td>Brain</td>
<td>Dead</td>
</tr>
<tr>
<td>10</td>
<td>56/F</td>
<td>10 cm/470 g</td>
<td>CS</td>
<td>3/10HPF</td>
<td>+/-</td>
<td>Liver</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>38/F</td>
<td>13.5 cm/380 g</td>
<td>Free cortisol ↑</td>
<td>Presence</td>
<td>+/-</td>
<td>Lung</td>
<td>Alive</td>
</tr>
<tr>
<td>12</td>
<td>Adult/M</td>
<td>22 cm/2,000 g</td>
<td>-</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Liver</td>
<td>Unknown</td>
</tr>
<tr>
<td>13</td>
<td>26/F</td>
<td>8 cm/185 g</td>
<td>Slight hypertrichosis</td>
<td>Unknown</td>
<td>+/-</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>14</td>
<td>49/M</td>
<td>6 cm/unknown</td>
<td>-</td>
<td>4-5/10HPF</td>
<td>+/-</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>15</td>
<td>64/M</td>
<td>8.8 cm/110 g</td>
<td>-</td>
<td>Rare</td>
<td>+/-</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>16</td>
<td>61/M</td>
<td>10 cm/192.8 g</td>
<td>Free cortisol ↑</td>
<td>&gt;25/50HPF</td>
<td>+/-</td>
<td>Lung, liver</td>
<td>Dead</td>
</tr>
<tr>
<td>This case</td>
<td>43/F</td>
<td>8 cm/347 g</td>
<td>CS</td>
<td>4-5/10HPF</td>
<td>+/-</td>
<td>Lung</td>
<td>Alive</td>
</tr>
</tbody>
</table>

PA, Pituitary adenoma; PH, Parathyroid hyperplasia; CS, Cushing syndrome.

Fig. 1. Computerized tomography of abdomen and pelvis (A) showed a large centrally necrotic mass replacing left adrenal gland and abutting on pancreas head. In left adrenalectomy specimen (B), the adrenal gland was entirely replaced by a necrotic solid mass and cut surface was lobulated and largely necrotic. The viable tumor in the periphery was semitransparent and myxoid, intermixed with bright yellow areas.
right hemihepatectomy was done due to multiple metastatic nodules in the liver.

On gross examination, the adrenal gland measured $8 \times 6 \times 6$ cm and it weighed 347 g. The adrenal gland was nearly replaced by the tumor, and this tumor was multinoddy and covered by a thin capsule. A normal adrenal gland could not be identified grossly. The cut tumor surface was vaguely nodular due to fibrous septa and it showed pale yellowish semitransparent and myxoid areas and bright yellow areas; it was centrally hemorrhagic and had necrotic foci (Fig. 1B).

Histologically, the cellularity of the tumor was variable according to the amount of the myxoid stromal components. Areas with myxoid material occupied about 80% of the viable tumor. They were intermingled with areas of conventional adrenal cortical carcinoma. The tumor cells in the myxoid areas were smaller than those of a conventional tumor and they were arranged in anastomosing cords, trabeculae or cribriform patterns according to the myxoid stroma (Fig. 2A). Focal areas showed pseudoglandular architecture. The tumor cells in the myxoid area were small and round, and they had rather condensed nuclei and scant eosinophilic cytoplasm. The cellular pleomorphism was milder in this area, but mitotic figures were 4-5/10 HPFs, similar to those of the conventional area. However, the cells with karyorrhectic or pyknotic nuclei were very frequent in the myxoid area (Fig. 2B-E). The tumor cells in the conventional area were relatively large in size and they had hyperchromatic nuclei with marked variation of nuclear size, and clear or eosinophilic abundant granular cytoplasm. The myxoid stroma was positive for alcian blue stain, but it was negative for periodic acid-Schiff (PAS) stain (Fig. 3A, B). The tumor extended to the periadrenal adipose tissue areas through the adrenal capsule. Lymphovascular invasion was observed.

Table 2 shows all antibodies, dilutions, methods, clones and companies used for immunohistochemistry. On immunohistochemical staining, the cells were positive for vimentin, α-inhibin, and synaptophysin, but they were negative for pan-cytokeratin and CAM 5.2 (Fig. 3C, D). Chromogranin staining was not informative. The immunohistochemistry results were compatible with those of conventional adrenal cortical carcinoma. The Ki-67 labeling index was up to 10% in the highest area, and this was 2 times higher in the conventional areas than that in the myxoid areas (Fig. 3E, F). Neither metastasis nor direct inva-

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**Fig. 2.** Conventional adrenal cortical carcinoma component (left) and myxoid component (right) were intermixed. In myxoid area, tumor cells were smaller than those in conventional area (A). Several morphologic patterns are observed in the myxoid area of the tumor. The stromal myxoid material made tumor cells arranged in cords (B), pseudoglandular (C), cribriform (D) or freely floating (E).

**Table 2.** Antibodies used in immunohistochemical Staining

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Dilution factor</th>
<th>Method</th>
<th>Clone</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>Ready-to-use</td>
<td>pH6.0 15 min 98°C</td>
<td>E29/EP1</td>
<td>DAKO</td>
</tr>
<tr>
<td>Inhibin</td>
<td>× 100</td>
<td>pH9.0 15 min 98°C</td>
<td>R1</td>
<td>Serotec</td>
</tr>
<tr>
<td>CAM 5.2</td>
<td>× 50</td>
<td>pH6.0 15 min 98°C</td>
<td>35 pH12</td>
<td>DAKO</td>
</tr>
<tr>
<td>CK, pan</td>
<td>× 50</td>
<td>Auto, 1-4 min, Protease</td>
<td>AE1/AE3</td>
<td>DAKO</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Ready-to-use</td>
<td>Mild 32 min</td>
<td>3B4</td>
<td>DAKO</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Ready-to-use</td>
<td>No</td>
<td>Poly</td>
<td>DAKO</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>× 300</td>
<td>pH6.0 15 min 98°C</td>
<td>Poly</td>
<td>DAKO</td>
</tr>
<tr>
<td>Ki-67</td>
<td>× 50</td>
<td>pH6.0 15 min 98°C</td>
<td>MIB-1</td>
<td>DAKO</td>
</tr>
</tbody>
</table>
sion was found in the distal pancreas and spleen, although these organs were inseparable on the operation due to tight adhesion.

Five months later, 4 metastatic nodules in the liver were removed. Among them, the three larger nodules ranged from 1 cm to 2.5 cm in size and they showed conventional histology, and the smallest one was 0.5 cm in size and it had myxoid stroma like the primary tumor.

**Fig. 3.** Myxoid component was negative in PAS stain (A) but positive in alcian blue stain (B). In immunohistochemical stains, the tumor is positive for α-inhibin (C) and synaptophysin (D) both in areas of conventional and of myxoid components. Ki-67 labeling index was in the range of 5-10%, higher in area of conventional histology (E) than in myxoid area (F).

**DISCUSSION**

Adrenocortical carcinoma occurs in about 0.5 to 2 cases per 1,000,000 patients yearly. The most common clinical presentation, such as Cushing syndrome and/or virilization, is related to glucocorticoid and androgen production by the tumor. Usually, adrenocortical carcinoma recapitulates the normal adrenal
cortex, which is characterized by such architectural features as sheets of cells interrupted by sinusoidal networks and the cyto-
ological features of large polygonal cells with abundant clear to
eosinophilic granular cytoplasm and a variable degree of nucle-
ar pleomorphism. With these characteristic features, the diag-
nosis of adrenocortical neoplasm is not difficult, although differenti-
ating benign tumor from malignant tumor is the greatest
concern.10 Our case can be easily categorized as carcinoma because
the tumor showed many of the histologic criteria of malignan-
cy proposed by Weiss et al.10

There are only a few histologic variants of adrenal cortical
tumors, and myxoid variant is one of these. It is difficult to diag-
nose them precisely due to their rarity. Myxoid change can occur
in adrenocortical carcinoma and adenoma.3,11,12 Brown et al.3
reviewed 300 adrenocortical neoplasms from the Mayo Clinic
from 1965 to 1984; less than 3% of the carcinomas and 1% of
the adenomas had myxoid components. There have been only
such sixteen case reports since Tang et al.1 reported on myxoid
adrenocortical carcinoma in 1979.1,9,3 There have been no reported
cases of myxoid adrenocortical carcinoma in the Korean literature.
In 2004, Song et al.13 published four cases of oncocytic adreno-
cortical carcinoma, and two of these showed myxoid change.
They mentioned that myxoid change was associated with cystic
and fibrous change of the tumor and their main neoplastic ultra-
structural components were oncocytes that contained abundant,
eosinophilic, granular cytoplasm, with compactly arranged mito-
ochondria and tubular cristae. In our case, ultrastructural exami-
nation was not performed, but there didn’t seem to be an area
with such features.

The percentage of the myxoid component in this neoplasm
is variable, from 10% to 100%, in the reported cases. The area
of conventional adrenocortical carcinoma morphology can be
absent.2 Due to the myxoid materials in the stroma, several archi-
lectual patterns of the tumor are transformed or exaggerated,
and these show anastomosing cords, cribriform, sheets or nests,
or these structures are freely floating in copious amount of acel-
lar myxoid materials. The myxoid material is characteristically
positive for alcian-blue stain, but it is usually negative for
mucicarmine or PAS stains. Myxoid adrenocortical carcinoma
can show extensive lipomatous metaplasia or a pseudoglandular
pattern.3,4 Adrenocortical carcinoma can have gelatinous (‘my-
roid’) and friable thrombi in the vena cava.14 When myxoid
adrenocortical carcinoma does not have area of conventional cor-
tical carcinoma, the following tumors should be included in the
differential diagnosis: myxoid liposarcoma, myxoid leiomyma
and leiomyosarcoma, chordoma, myxoma, lipoma and epithe-

The pathogenesis of myxoid change is not clear. Honda et al.11
said that adrenal cortical cells produced myxoid material because
they originated from mesoderm. Similarly, myxoid liposarcoma,
myxoid malignant fibrohistiocytoma and malignant mesothe-
loma can make mucin of the connective tissue type. However,
there has been no case demonstrating intracellular mucin by
special stains or ultrastructural examination. Forshoefel et al.2
proposed that the mucin came about by a degenerative process
or because of mucin production by stromal fibroblasts. The cases
of Forsthoefel’s3 and Karimi’s9 also showed hormonally active
tumors in spite of their extensive myxoid change (>70% and
100%, respectively). The suggestion that myxoid material is
actively produced by the tumor rather than by a degenerative
process seems to be more appropriate, but further clarification
is needed. The tumor cells were consistently relatively smaller
in size with a shrunken appearance in the previously reported
cases and our case.3,9 In our case, the findings of rather condensed
chromatin patterns, many karyorrhectic or pyknotic nuclei and
a lower ki-67 labeling index as compared to those of the conven-
tional area are all indicative of a degenerative process for this
tumor. However, it is not supportive of a degeneration patho-
genesis that the smallest metastatic nodule in the liver of this
patient showed myxoid change and the original tumor was func-
tionally active. Because the biologic behavior of a myxoid adreno-
cortical neoplasm is known not to differ from that of the conven-
tional histology, more cases will be needed to characterize
this special variant.

It is uncertain whether myxoid change is associated with the
tumor’s malignant potential. This is the first such reported case
for carcinoma and myxoid change is more frequent in carcino-
mas than in adenomas in the reported cases,3 but it is too rare to
evaluate any clinicopathologic relationship. Tang et al.1 sug-
goed that it should be related to malignant behavior because of the
invasiveness, metastasis and high proliferating cell nuclear anti-
gen positivity. Peterson et al.15 reported that myxoid adrenocor-
tical carcinoma showed more malignant behavior in the domes-
tic ferret because the tumor was larger in size with more chance
for metastasis than that of the conventional adrenocortical car-
cinoma.15 But the others proposed there was no correlation be-
tween myxoid change and aggressiveness.3 It is interesting that
the myxoid variant showed a distinct gene expression for the
transcriptional profiles as compared to the other adrenocortical
carcinomas.5,6 In our case, there were more mitotic figures in
the conventional area than those in the myxoid area. However,
simple comparison of mitotic figures is not reasonable to assess
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the biological aggressiveness.

Since many epithelioid mesenchymal neoplasms with myxoid change can occur in the retroperitoneum, myxoid variant of adrenocortical neoplasm can be part of the differential diagnoses despite of its rarity.

REFERENCES