Neuroblastoma arising in a mature cystic teratoma of the ovary

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SUMMARY A case is described of a neuroblastoma which appeared to arise in a mature cystic teratoma of the ovary. The literature concerning neural tumours of the ovary is briefly reviewed and the grounds for believing that the development of such neoplasms is an indication of the presence of immature neuroepithelial components in a teratoma, rather than a result of malignant change in a fully mature teratoma, are discussed.

We describe here the clinical and pathological features of a neuroblastoma which arose in a mature cystic teratoma of the ovary, this being, we believe, the first authentic example of malignant change of this type occurring in an otherwise fully benign ovarian teratoma.

Case report

An 18-year-old girl presented with complaints of cramp-like lower abdominal pain for eight months, urinary frequency for six months and bleeding per vaginam for 10 days. Eighteen months previously she had born a full-term normal infant and since then had been on oral contraceptives. Menstruation had been previously regular and her only previous illness was acute appendicitis as a child. On examination, a pelvic mass the size of an 18-week gravid uterus was palpable. The uterus itself was of normal size and retroverted. There were no other abnormal physical findings and sonography showed a large left sided multilocular mass. At laparotomy an apparently cystic mass measuring approximately 10 cm in diameter was found replacing the left ovary and a left salpingo-oophorectomy was performed. A "dermoid cyst," measuring 5 cm in diameter, was found arising in the right ovary and this was enucleated with conservation of the right ovary and tube. The patient made a good recovery from surgery and was well on discharge 12 days later.

Pathological findings

Macroscopic appearances

The left ovarian tumour was a grey-brown, fluctuant mass measuring 10 × 10 × 8 cm. The outer surface was smooth and free of adhesions and the capsule appeared intact. On cross-sectioning, it was apparent that the tumour was partially formed of a typical mature cystic teratoma, measuring 5 cm in diameter, which contained hair and sebaceous material. The remainder of the tumour consisted of a multilocular, partially cystic structure which enveloped the cystic teratoma.

The central part of this was largely necrotic but the peripheral portion consisted of locules, mostly measuring 1 to 2 cm in diameter, which were separated and lined by friable pale brown tissue. The lesion from the right ovary was a macroscopically typical small mature cystic teratoma.

Light microscopy

Histological sections from the left ovarian mass showed two distinct elements. The mature cystic teratoma identified macroscopically was lined by keratinising stratified squamous epithelium with associated pilosebaceous follicles and occasional apocrine glands. Foci of mucus-secreting columnar epithelium, bone and a tooth were also present. The second element, which closely invested the cystic teratoma, was a densely cellular neoplasm with central areas of cystic degeneration (Fig. 1). The tumour was surrounded by a thick fibrous capsule from which a few fibrous trabeculae entered the neoplastic mass, but generally the large masses of cells were poorly supported by stroma. The tumour was markedly vascular and the thin-walled vessels were supported by delicate fibrous septa which tended to separate the tumour cells into alveolar masses. Areas of haemorrhage were numerous, particularly towards the centre of the tumour. The predominant tumour cell was small with a round or polygonal, darkly staining nucleus with closely clumped chromatin and rarely discernible eosinophilic cytoplasm. These cells were interpreted as
Fig. 1  Low-power photomicrograph showing at the top of the picture the typical squamous epithelium with attached pilosebaceous follicles of the dermoid cyst and at the bottom of the picture the densely cellular neuroblastoma which completely invested the dermoid cyst. Haematoxylin and eosin × 23

Fig. 2  High power detail of rosette showing sympathogonia. Glycol methacrylate, haematoxylin and eosin × 576
Fig. 3  Neuroblastoma showing varying size of cells. A clump of sympathoblasts is present in the middle of the field. Glycol methacrylate, haematoxylin and eosin x 576

Fig. 4  One of the very few areas in which ganglionic differentiation is present. Glycol methacrylate, haematoxylin and eosin x 225
Neuroblastoma arising in a mature cystic teratoma of the ovary

Fig. 5 General low power view of tumour showing rosettes and neurofibrillary substance. Haematoxylin and eosin × 225

neoplastic homologues of sympathogonia (Fig. 2). In some parts of the tumour clumps of cells with larger, lighter staining, vesicular nuclei and more substantial eosinophilic cytoplasm were seen. The cell borders were indistinct, producing a pseudosyncytial appearance. These cells were interpreted as being homologous with sympathoblasts (Fig. 3). In a very few areas, large cells with voluminous eosinophilic cytoplasm and a single, round, pale staining, vesicular nucleus containing a prominent nucleolus were present and these were interpreted as evidence of minimal ganglionic differentiation (Fig. 4).

The arrangement of tumour cells was generally haphazard but rosette formation was obvious in most parts of the neoplasm. The rosettes consisted of a ring of round or oval cells with tail-like cytoplasmic processes projecting inwards. In a few areas neurofibrillary material was abundant and formed small eosinophilic strands and islets (Fig. 5). The tumour was confined within the capsule with no evidence of capsular invasion. Tumour emboli were, however, seen in hilar lymphatics.

The right ovarian tumour was a mature cystic teratoma which did not contain any neural elements.

Electron microscopy

Electron microscopic examination was made on formalin-

Fig. 6 Electron micrograph of tumour cells showing neurosecretory granules. × 153 000
fixed tissue. There was considerable loss of cytological
and organelle detail but neurosecretory granules were
seen in a small proportion of the tumour cells (Fig. 6).

CLINICAL FOLLOW-UP
The patient has so far been followed up for some 12
months as an outpatient. Twenty-four hour urine samples
were collected postoperatively and the urinary excretion
concentrations of vanillyl methoxymandelic acid (VMA),
homovanillic acid (HVA), free and conjugated normetadrenaline (NMA) and free and conjugated metadrenaline (MA) were measured. The results are shown in the Table. The rising concentrations of VMA, HVA and NMA are thought to indicate the presence of metastatic tumour, and at time of writing further diagnostic procedures are planned. Indefinite follow-up will be pursued.

Discussion
Malignant change occurs in between 1 and 2% of mature
cystic teratomata of the ovary and whilst in theory any
type of malignant neoplasm can arise in a previously
benign teratoma, the vast majority which do occur are in
practice squamous cell carcinomatosa, most of the remain-
der being adenocarcinomatosa. Neural tissue occurs with
considerable frequency in mature cystic teratomata but
the development of a malignant neural neoplasm in an
ovarian tumour of this type is an event of exceptional
rarity. There has, however, been one indisputable example
described of a grade 4 astrocytoma arising in a mature
cystic teratoma of the ovary whilst there have been four
previous reports of a neuroblastoma developing in an
ovarian mature cystic teratoma. The validity of these
latter cases does not, however, withstand critical scrutiny
for three of the reported tumours would more correctly
be interpreted as teratomata containing immature
neuroepithelial elements, some of which had a neuroblas-
tomatous appearance whilst the fourth was an immature
(malignant) teratoma which contained, inter alia, imma-
ture neuroepithelial tissue and gave rise to metastases
containing multiple tissue elements, some of which were
neural with a neuroblastomatous component. In none of
these cases was there any real evidence of malignant
change having occurred in a previously fully benign
teratoma and in none was a definite tumour mass,
showing the histological features of a neuroblastoma,
present.

Recently, however, Aguirre and Scully have reported
five malignant neural tumours of the ovary, four of which
appeared to be primary ovarian neoplasms and one of
which was possibly a metastasis from an adrenal neuroblastoma.
Of the four definitely primary ovarian tumours, one was
classified as a primitive neuroectodermal neoplasm with
ependymal, neuroblastic and glial differentiation and
seconds as a primitive neuroectodermal tumour with
ependymal and glial differentiation and medulloepithe-
lioma. The remaining two tumours resembled an
glioblastoma multiforme. In one of these cases there was
no evidence of any other teratomatous elements whilst in
another the ovarian tumour was devoid of non-neural
tissue components but gave rise to metastases containing
cartilage. The remaining two cases, both classed as
neuroblastoma, were associated with mature, but relatively
inconspicuous, non-neural tissue elements and appeared
to have developed in mature cystic teratomata. It is of
interest that these latter two cases had a macroscopic
appearance similar to that of the tumour reported here in
so far as the malignant neural tumour appeared to envelop
the cystic teratoma rather than being confined within it.
Aguirre and Scully comment on the diagnostic problems
posed by a pure, or largely pure, malignant neural
neoplasm arising in the ovary and upon the possible
confusion with a granulosa cell tumour.

It would appear therefore that the tumour described
here is the first definite example of a neuroblastoma
which has arisen in a mature cystic teratoma of the ovary.
The purist, however, would maintain, with considerable
validity, that a neuroblastoma cannot arise in a fully
mature teratoma and the development of a malignant
neural tumour indicates that immature neuroepithelial
elements must have been present in the otherwise mature
teratoma. This view would accord with the age distribu-
tion of malignant neural neoplasms of the ovary. Our
patient was, as were all those in other acceptable cases
less than 20 years of age, this being the typical age group
in which immature, and hence malignant, ovarian
teratomata occur. By contrast, malignant change in a fully
mature ovarian teratoma occurs most commonly during
the fifth and sixth decades, this age-related pattern
lending support to the view that a malignant neural
neoplasm can only arise from immature neuroepithelial

tissue in an ovarian teratoma.

The prognosis for patients with a malignant neural

tumour of the ovary is gloomy, three of the four patients
reported by Aguirre and Scully died, all within four years
of surgical removal of the primary neoplasm, whilst the
patient described by Shirley, Piro and Crocker died 11
months after oophorectomy. Ganglionic differentiation
in neuroblastomas elsewhere in the body is associated with a
relatively better prognosis but the very minimal degree of

ganglionic differentiation present in this case is not

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### Postoperative urinary biochemical markers

<table>
<thead>
<tr>
<th></th>
<th>VMA (μmol/24h)</th>
<th>HVA (μmol/24h)</th>
<th>NMA (μmol/24h)</th>
<th>MA (μmol/24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>9-36</td>
<td>10-40</td>
<td>0.55-2 73</td>
<td>0.25-1 78</td>
</tr>
<tr>
<td>7 weeks post-op</td>
<td>25</td>
<td>21</td>
<td>3.1</td>
<td>0-7</td>
</tr>
<tr>
<td>12 weeks post-op</td>
<td>48</td>
<td>26</td>
<td>5.4</td>
<td>1-0</td>
</tr>
<tr>
<td>7 months post-op</td>
<td>245</td>
<td>105</td>
<td>7-1</td>
<td>1-1</td>
</tr>
<tr>
<td>11 months post-op</td>
<td>310</td>
<td>130</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(3 consecutive days)</td>
<td>188</td>
<td>88</td>
<td>8.7</td>
<td>0.8</td>
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thought to be significant. The patient described in this report is currently well but biochemical tests indicate that metastatic tumour is probably present.

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References


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