Brenner tumour of the vagina

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broad ligament, 5-7 the uterus, 8 the vagina, 9 and the
testicular and para-testicular tissues. 10-12
For a diagnosis of Brenner tumour, both in-
tegral components (the epithelial and me-
senchymal stroma) must be present. 2,7,8

There is only one documented case of ex-
traovarian Brenner tumour of the vagina in the
literature. 9 A similar case, however, has been
reported by Buntine et al 13 who called the polyp
"benign mixed mullerian tumour of the vagina" and
pointed out its resemblance to Brenner

Shchevchuk et al, 4 in their case of "malign-
nant mixed tumour of the vagina", were prob-
ably describing a malignant Brenner tumour.
The authors commented that the ultra-
structural findings of their case confirmed
urothelial differentiation and that the tumour
appeared to arise from mesonephric remnants.
It seems that the reason for the confusion in the
nomenclature of this neoplasm is because of its bi-
 or triphasic nature.

The histogenesis of Brenner tumour is still
troversial. 2,6,13 The important proposed sites
of origin include ovarian surface epithelium 5,9,11; remnants of embryonic coelomic epithe-
lium 6,11; displaced mesothelium 9,12; rests of
Waltbard's cells 9,12; and remnants of muller-
ian, 9-12 mesonephric, 10,11,12 or wolffian
ducts. 4,9,10,11,12 Other less likely possible sources
are as follows; ovarian stroma 2,8,12; rette
ovaria 2,13; rette testis 12; germ cell (teratomatous
derivation) 12,13; granulosa cells 1; ectopic (ac-
cessory) ovarian tissue 6; ovotesticular 12; and ves-
tibular glands of the vagina. 9

The presence of the tumour in men and at
sites far away from the ovary indicates that this
neoplasm is not invariably of ovarian origin.
The concept of this neoplasm originating from

ovarian coelomic epithelium via a process of wolffian differentiation has been supported by
serial reconstruction studies, by its coexistence with other ovarian tumours, and by ultra-
structural studies. 13 Remnants of the wolffian
ductal system are known to occur in the broad
ligament, cervix and vagina, and must be ser-
iously regarded as an alternative source of the
neoplasm in an extraovarian site. 2 This theory
is supported by fact that the tumour is biphasic
and that it resembles the transitional epithelium
lining the genitourinary tract.

A Brenner tumour of the vagina could there-
fore be derived directly from wolffian remnants
at this site or could originate from mullerian
ductal tissue which forms the upper part of the
vagina, by a process of wolffian metaplasia.


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P-glycoprotein positive, drug resistant invasive
lymphoepithelial thymoma: treatment response
to chemotherapy with cyclosporin and quinine

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Abstract
A case of invasive drug resistant thymoma,
expressing P-glycoprotein, which showed
noticeable clinical response to chemother-
apy and the multidrug resistance
modulating agents cyclosporin and quin-
ine is reported. A 46 year old man pre-
sented with severe left shoulder pain and a
diagnosis of invasive lymphoepithelial
thymoma was made following chest x-ray
and a computed tomography scan. The
patient underwent extensive chemo-
therapy without resolution of the tumour.
More than 90% of the malignant epithelial
cells were strongly positive for P-glyco-
protein and based on this observation,
cyclosporin and quinine were added to the
chemotherapy regimen. The mediastinal
mass completely resolved and the size of
the pleural metastasis decreased sub-
stantially. The patient, however, died of
an intercurrent infection. This case report
highlights the feasibility and efficacy of
using cyclosporin and quinine in com-

1 Brenner F, Dsophoroma folliculare. Frank Zeitschr Path
1907;1:150-71
2 Pschers H, Wilkstrom B. Extraovarian tumour coexisting with
3 Buntine DW, Henderson PS, Bagg JSG. Benign mullerian
4 Shchevchuk MM, Fenoglio CM, Latres R, Frick HC, Richter
MH. Malignant mixed tumor of the vagina probably arising
5 Robinson TG. Extraovarian Brenner tumor. Obstet Gynecol
1950;57:890-1.
6 Hampton HL, Huffman HT, Meeks RG. Extraovarian Bren-
7 Wagner I, Bettendorf U. Extraovarian Brenner tumour. Case
8 Arthiger RH, Bocian JJ. Brenner tumor of the uterus. Cancer
9 Chen KTK. Brenner tumor of the vagina. Diagn Gynecol
26:835-6.
722-6.
12 Young RH, Scully RE. Testicular and paratesticular tumors
and tumor-like lesions of ovarian common epithelial and
mullerian types. A report of four cases and review of the
13 Balasa RW, Adcock LL, Prem KA, Dehner LP. The Brenner
50:120-8.

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bination with VAD chemotherapy in the
treatment of invasive thymoma.

Keywords: Invasive thymoma, multidrug resistance, P-
glycoprotein expression.

Thymoma is the commonest type of tumour in the anterior–superior mediastinum, especially in middle-aged or older adults. It is usually a slow growing tumour with benign histology, but it can behave aggressively and invade the surrounding tissues. The standard therapy is local surgery and irradiation. Adjuvant chemotherapy has been used in invasive thymomas. However, recurrences within the thorax are frequent and the mechanisms of resistance to chemotherapy are unclear. We report a case of an invasive drug resistant thymoma which expressed P-glycoprotein and showed noticeable clinical response to administration of chemotherapy (VAD) and quinine/cyclosporin, multidrug resistance modulating agents.

Case report

A 46 year old man presented initially with severe left shoulder pain. Chest x ray and a computed tomography scan demonstrated an anterior mediastinal mass invading the pleura and adjacent lung. The diagnosis of invasive lymphoepithelial thymoma was made on a thoracotomy biopsy. Following incomplete resection, the patient was treated with four courses of ProMACE-MOPP (Pro-prednisolone, M-methotrexate, A-doxorubicin, C-cyclophosphamide, E-etoposide, followed by M-mechloethamine, O-vincristine, P-procarbazine, P-prednisolone). After an initial partial response, rapid tumour progression was seen. Radiotherapy (60 Gy) was administered to the mediastinum and left hemithorax. This was followed by the administration of etoposide (VP16, 200 mg intravenously on days 1 to 3), cisplatin (200 mg intravenously on day 1) and ifosfamide (3 g intravenously on days 1 to 3). A total of five courses was given with no response. Severe pancytopenia and two episodes of septicaemia complicated the treatment. Interferon was then administered with the dosage escalated to 10 × 10³ units/day five times weekly, in combination with three courses of high dose ifosfamide (1.5 g/m² intravenously on days 1 to 5 every four weeks). No decrease in tumour size was observed and interferon was not administered further. At that stage, an isolated pulmonary lesion developed in the upper lobe of the left lung (fig 1A); a fine needle biopsy confirmed the invasion by a lymphoepithelial thymoma. Immunoperoxidase assay on cryostat sections, using the monoclonal antibodies directed against cytokeratin (39 kDa) and CD1 (Leu 6) identified the thymic malignant epithelial cells and cortical lymphocytes, respectively. More than 90% of the malignant epithelial cells examined were strongly positive for P-glycoprotein by alkaline phosphatase–antialkaline phosphatase assay using the monoclonal antibody JSB-1 as previously reported (fig 2).¹

Based on these results, the multidrug resistance (MDR) modulating drugs, cyclosporin and quinine, were added to the chemotherapy regimen (VAD, vincristine, doxorubicin and dexamethasone). Cyclosporin was given as an intravenous bolus injection (4 mg/kg) for 24 hours before the VAD infusion on day 0, then as a continuous infusion until day 6 at a dosage of 8–10 mg/kg. The dose was adjusted to achieve a whole blood cyclosporin concentration above 1500 μg/l. Quinine was given as a bolus dose of 7.5 mg/kg and as a continuous infusion for six days at a dose of 4–7 mg/kg according to the patient’s tolerance. The average daily whole blood cyclosporin concentration and plasma quinine concentration were 1600 μg/l and 8 mg/l, respectively. After three cycles of therapy, complete resolution of the mediastinal mass.

Figure 1 X ray before (A) and after (B) three cycles of VAD chemotherapy and MDR modulating agents (cyclosporin/quinine).
and a significant reduction in the size of the pleural metastasis was observed radiologically (figs 1A and 1B). The patient received four courses of this therapy without significant side effects, except cinchonism. After completion of the fourth cycle, he died from an intercurrent infection whilst stationed in a neighbouring country. A postmortem examination was not performed.

Discussion

Although surgery and local radiotherapy are the accepted therapy for thymoma, chemotherapy has been used for invasive and incompletely resected thymoma. Studies have shown that doxorubicin, epirubicin, cyclophosphamide, or ifosfamide, cisplatin, bleomycin, and etoposide are effective chemotherapeutic agents.\(^2\)\(^-\)\(^4\) Overall, the place of chemotherapy and the optimal combination of drugs in the treatment of thymoma are still being evaluated. In lymphoepithelial and epithelial cell predominant thymomas, which are the commonest histological types,\(^5\) the cortical differentiation of the malignant epithelial cells is correlated with a poor response to therapy and a bad prognosis\(^6\)\(^-\)\(^7\) but the mechanisms of resistance are unclear.

The MDR, P-glycoprotein phenotype has been shown to be associated with chemotherapy failure in a wide range of haematological malignancies and solid tumours.\(^8\) The resistance of this cortical thymoma to chemotherapy could be related to P-glycoprotein expression. To our knowledge, this is the first report of P-glycoprotein expression in the malignant epithelial cells of an invasive thymoma. In this patient the accumulated doses of VP16, doxorubicin and vincristine were 4920 mg, 400 mg and 16 mg, respectively. These dose levels are reported to be associated with a high incidence of P-glycoprotein expression following chemotherapy in multiple myeloma.\(^9\) Because of insufficient initial biopsy material, the issue of whether P-glycoprotein was expressed by the epithelial cells initially or whether this expression was induced by chemotherapy could not be addressed.

Cyclosporin, for multiple myeloma,\(^10\) and verapamil, for lymphoma,\(^11\) have been used in the clinical setting as MDR modulating agents. Quinine has been demonstrated to be another non-cytotoxic agent that can act as an MDR modulating agent.\(^12\) In our patient the tumour was extremely resistant to a wide combination of chemotherapeutic agents, including doxorubicin, vincristine and steroids which are associated in the VAD regimen. This clinical drug resistance together with P-glycoprotein expression by the malignant epithelial cells prompted us to add cyclosporin and quinine to the VAD regimen. Regression of the thymoma was obtained after three cycles of therapy and no significant side effects due to cyclosporin and quinine were observed.

In conclusion, this case report illustrates an invasive thymoma which was resistant to multiple chemotherapeutic agents and expressed high concentrations of P-glycoprotein. It also highlights the feasibility and efficacy of using cyclosporin and quinine in combination with VAD chemotherapy in the treatment of invasive thymoma. Further studies are required to confirm these observations.

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