Brenner tumour of the vagina

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

Abstract
A case of invasive drug resistant thymoma, expressing P-glycoprotein, which showed noticeable clinical response to chemotherapy and the multidrug resistance modulating agents cyclosporin and quinine is reported. A 46 year old man presented 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 chemotherapy without resolution of the tumour. More than 90% of the malignant epithelial cells were strongly positive for P-glycoprotein 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 substantially. The patient, however, died of an intercurrent infection. This case report highlights the feasibility and efficacy of using cyclosporin and quinine in com-
bination with VAD chemotherapy in the treatment of invasive thymoma.

(F Clin Pathol 1995;48:679–681)

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 ProMAC-MOPP (Pro-prednisolone, M-methotrexate, A-doxorubicin, C-cyclophosphamide, E-etoposide, followed by M-mechlorethamine, 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 septicemia complicated the treatment. Interferon was then administered with the dosage escalated to $10^6$ 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).

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) 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.1-4 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 chemotherapeutic 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.

This study was supported by the Fonds National de la Recherche Scientifique (Grant Télévie no 7.4575.91), the Loterie Nationale and the Salus Sanguinis Foundation.