# Doxil-induced regression of pleuro-pulmonary metastases in a patient with malignant meningioma

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**Metastatic meningioma is a rare disease, which has no effective chemotherapy. We report on a treatment of this condition with Doxil, a liposomal doxorubicin formulation. A 60-year-old woman with massive pleuro-pulmonary metastases from recurrent cranial meningioma was treated with Doxil (50–37.5 mg/m$^2$) for 18 months with near-complete resolution of metastases and disappearance of pleural fluid. The only significant toxicities observed were stomatitis and hand–foot syndrome, which resolved with dose reduction and increase of dosing intervals. Doxil was cleared very slowly in this patient with a monoexponential half-life of 108 h. The patient remains in near-complete response for 6 months after treatment discontinuation. This is the first report on an effective chemotherapy in a patient with typical metastatic meningioma. The exact mechanism accounting for such an effective drug action is not clear, but may be related to a particularly high microvascular permeability to the liposome carriers in these metastatic lesions.** *Anti-Cancer Drugs* **14:247–250 © 2003 Lippincott Williams & Wilkins.**

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## Introduction

Meningioma is one of the most common neoplasms of the central nervous system, comprising 15% of primary brain tumors. They are usually slow growing and benign, but 0.1% of meningiomas are malignant and metastasize, most commonly to the lung, followed in frequency of spread by liver, lymph nodes, bone, mediastinum and pleura [1–5]. Only about 100 cases of metastatic meningioma have been reported [1,3,6]; most of them as case reports because of the rarity of the disease. None of these reports has identified an effective chemotherapy for metastatic disease [4,6,7].

Doxil (Caelyx) is a formulation of pegylated liposomal doxorubicin with a prolonged circulation time and selective accumulation in tissues with increased vascular permeability, such as solid tumors. It has been approved for the treatment of AIDS-related Kaposi's sarcoma and recurrent ovarian cancer, and is effective in breast cancer and other tumors, including tumors outside the spectrum of free doxorubicin such as head and neck cancer (reviewed in [8]). According to two reports, Doxil appears to have tumoristatic and radiosensitizing activity in brain tumors [9,10]. Selective accumulation of Doxil in glioblastoma and brain metastases [9], and in preclinical models of brain tumor implants [11], has been shown.

We report here on a successful treatment of pleuro-pulmonary metastases from recurrent cranial meningioma with Doxil.

## Case report

In August 2000, a 60-year-old woman was admitted to hospital due to progressive dyspnea over the last month. Her medical history was remarkable for a diagnosis of (malignant) meningioma with the first craniotomy in 1981 (19 years prior to the current admission) and three more operations, the last one in 1992 (8 years prior to the current admission), for recurrent meningioma invasive to calvarian structures, with complete resection and adjuvant radiotherapy to the area. At the admission to the hospital, chest X-ray and chest computed tomography (CT) showed large right pleural effusion, and numerous bilateral pulmonary and pleural coin lesions of different size, the largest 8 cm in maximal diameter (Fig. 1A). FNA from a pulmonary lesion and cytology of pleural fluid showed malignant meningioma cells, with a microscopic tumor appearance similar to the original brain tumor. CT scan of the brain upon admission (and in follow-up examinations) showed no recurrence of the brain tumor. No other sites of metastases were found.

The patient underwent several pleural punctures for relief of the symptoms and was referred for treatment

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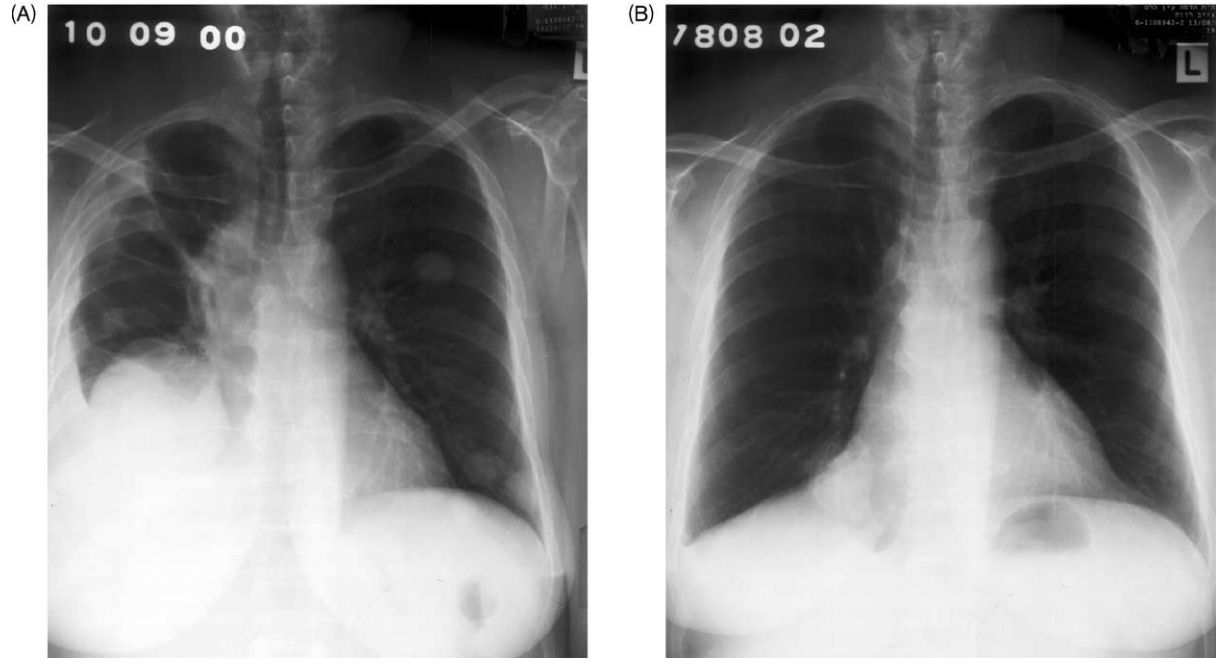
**Fig. 1**




(A) Chest X-ray at admittance after pleural puncture. Right pleural effusion is seen, as well as numerous bilateral pulmonary lesions, the largest one 8 cm in horizontal diameter. (B) Two years later. The pleural effusion and most of the lesions have disappeared; the largest one is now 3.5 cm in horizontal diameter. (Lesion size not corrected for film magnification factor.)

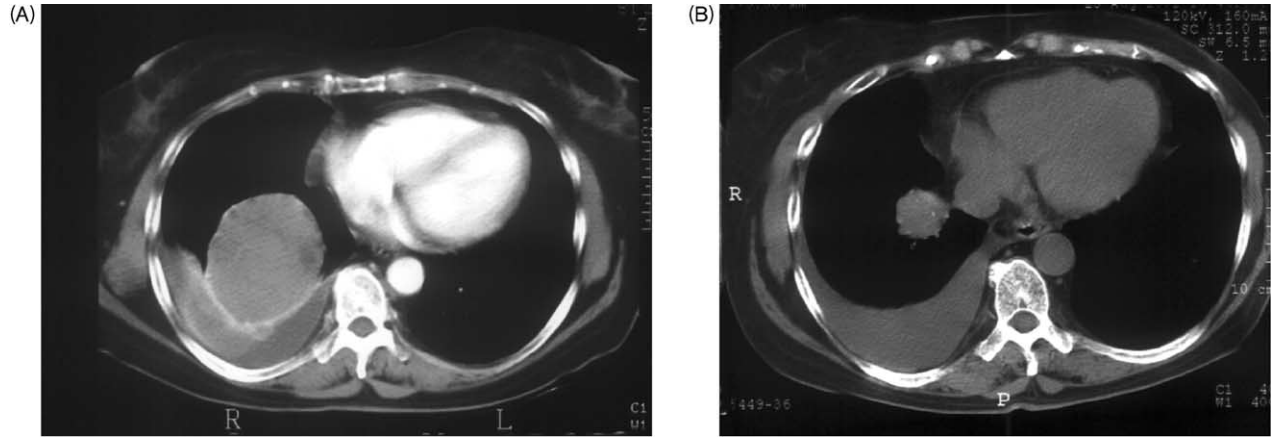
with Doxil within an experimental clinical study testing the cytoprotective effect of amifostine on Doxil-related toxicities.

The patient received 14 courses of Doxil on an ambulatory basis between September 2000 and March 2002: the first and second courses were given at a dose of 50 mg/m$^2$. Due to stomatitis, the following courses were given at reduced doses ranging from 45 to 37.5 mg/m$^2$. The first three courses were given on a 3-week schedule. Later on, the dose interval was lengthened gradually from 3 to 6 weeks, and in the last two courses to 8 weeks to allow for recovery of mucocutaneous (stomatitis, hand–foot syndrome) manifestations of Doxil-related toxicity and/or prevent their relapse. The first six courses were given with amifostine, 1000 mg, i.v. on day 1 of each cycle. The cumulative dose of doxorubicin was 670 mg/m$^2$ in 18 months. At this point it was decided to discontinue therapy because the patient had received a cumulative dose well above the current maximal recommendations for free doxorubicin (450–550 mg/m$^2$) and the Doxil–amifostine study had been closed, rendering problematic the supply of Doxil. After dose reduction and interval lengthening, stomatitis and hand–foot syndrome became milder, and, in some cycles of therapy, were absent. As to other signs of toxicity: myelosuppression, mostly neutropenia, was mild, without evidence of cumulative damage to bone marrow and without need for blood transfusions; there was no alopecia; and, most importantly, no evidence of cardiotoxicity based on clinical findings and good left ventricular function assessed by multigated angiocardiography scan prior, during and after Doxil therapy.

X-rays and CT scans of the chest (Figs 1 and 2) showed gradual reduction in the size of lesions and complete disappearance of all but one, the largest initial lesion in the right lower lobe, whose maximal diameter shrank from 7.8 to 2.8 cm. Most of the pleural effusion disappeared as well (Figs 1 and 2). CA-125, a blood tumor marker, gradually decreased from 493 U upon diagnosis to 230 U after six courses and to 15 U, within the normal range, at the end of the treatment. The patient remains stable with no radiographic signs of tumor regrowth for 6 months after the treatment was ended (Fig. 1B).

During the first course of Doxil, blood samples were withdrawn to measure doxorubicin plasma levels as required by the study protocol within which this patient was treated. Table 1 shows the results of pharmacokinetic analysis, of which the most remarkable finding is the exceedingly long half-life (108 h). In a previous study [12], we have found that patients with a Doxil half-life

**Fig. 2**




(A) CT scan at admittance after pleural puncture (August 2000). Note the largest lesion (largest perpendicular diameters: 7.8 × 6.8 cm) with pleural effusion containing soft tissue lesions. (B) One year later (August 2001). CT slice 2 cm below showing the same lesion at its maximal diameter after significant shrinkage (largest perpendicular diameters: 2.8 × 2.8 cm); soft tissue pleural lesions are absent.

**Table 1 Pharmacokinetic analysis of plasma doxorubicin levels after the first course of Doxil[a]**

| Dose | $C_{max}$ | AUC | $T_{1/2}$ (SD) | CL | $V_{ss}$ |
|---|---|---|---|---|---|
| 50 mg/m$^2$ | 19.5 mg/l | 3043 mg h/l | 108 (4) h | 16.4 ml/h/m$^2$ | 2.6 l/m$^2$ |

[a]Monoexponential clearance as determined by non-linear least-squares analysis (Pkanalyst software; Micromath, Salt Lake City, UT). Doxorubicin extracted and analyzed from plasma samples by high-performance liquid chromatography and fluorimetric detection as previously reported [16]. Doxorubicinol levels, when detected, were only 3.6–3.9% of doxorubicin concentration.

exceeding 85 h have a 2.7-fold greater risk (hazard ratio) of developing moderate to severe hand–foot syndrome, as is the case of this patient.

## Discussion

Meningioma is generally a benign tumor, but under very rare circumstances it can metastasize. There are no predictive factors for the process, but the risk is higher in tumors showing histological signs of malignant features and invading the venous sinuses. Patients undergoing recurrent craniotomies are also at higher risk of hematogenous spread [1,3,4,5]. The histological subtype of meningioma and its location in the cranium do not seem to influence the probability of metastasis [2]. The interval from primary detection to first metastasis has been reported to be as long as 24 years [4,6]. Our patient was diagnosed to have pulmonary metastases 19 years after the initial diagnosis of meningioma and 8 years after the last craniotomy. Thus, her case is consistent with the biological behavior of metastatic meningioma. At the time of diagnosis of the metastases, she did not have any evidence of local intra-cranial recurrence, similarly to other reports [4,6,7] and suggesting that the hematogenous spread occurred at least 8 years before.

Because of the rarity of metastatic meningioma, it is usually reported as case reports, and no controlled study can be performed to establish an appropriate treatment. Most of the reported patients died a short time after the diagnosis, with or without chemotherapy [1,4,5]. The drugs used for chemotherapy, not always reported, differed, and included ifosfamide, doxorubicin, dacarbazine, cyclophosphamide, vincristine, etoposide and cisplatin [1,5,7]. No improvement with any of these treatments has ever been reported.

We treated our patient with Doxil initially at 50 mg/m$^2$, a dose recommended for treatment of recurrent ovarian cancer and other solid tumors [8]. Amifostine given alongside Doxil is unlikely to affect the anti-tumor effect since it has no anti-tumor effect of its own and does not interfere with the anti-tumor effect of Doxil in animal tumor models [13]. Although the patient was treated initially at a relatively high dose intensity of 16.7 mg/m$^2$/week ( = 50 mg/m$^2$ every 3 weeks), this is not a major factor accounting for the anti-tumor response since tumors continued to shrink after dose intensity was reduced. We hypothesize that the 'stealth' (long-circulating) properties of Doxil in this patient, as confirmed by pharmacokinetic analysis, and a high vascular permeability of meningioma lesions are likely to result in enhanced tumor delivery of liposomal drug and account for the dramatic response. Contrast enhancement is a well-known radiological feature of meningiomas that hints at high vascular permeability [14]. The ability of

stealth liposomes to accumulate in tumors based on the enhanced permeability and retention phenomenon [8] has been documented in human tumors [15], including human brain tumors [9]. Therefore, it is conceivable that metastatic lesions may have been selectively targeted by Doxil, resulting in high and sustained tumor levels of doxorubicin which could mediate anti-tumor and anti-angiogenic effects leading to tumor regression.

In addition to tumor regression, another positive aspect of this case is the fact that, except for well-known mucocutaneous manifestations, the patient was able to tolerate therapy without any apparent life-threatening or cumulative toxicities, without transfusions and without hospital admissions.

## Conclusions

Our recommendation, based on this single, but very positive experience, is to consider treatment with Doxil as one valuable option in the management of metastatic meningioma.

## References


1 LeMay DR, Bucci MN, Farhat SM. Malignant transformation of recurrent meningioma with pulmonary metastases. *Surg Neurol* 1989; **31**:365–368.

2 Baisden BL, Hamper UM, Ali SZ. Metastatic meningioma in fine-needle aspiration (FNA) of the lung: cytomorphologic finding. *Diagn Cytopathol* 1999; **20**:291–294.

3 Figueroa BE, Quint DJ, McKeever PE, Chandler WF. Extracranial metastatic meningioma. *Br J Radiol* 1999; **72**:513–516.

4 Adlakha A, Krishna R, Adlakha H, Perry A, Crotty TB, Scheithauer BW, *et al.* Meningioma metastatic to the lung. *Mayo Clin Proc* 1999; **74**:1129–1133.

5 Safneck JR, Halliday WC, Quinonez G. Metastatic meningioma detected in pleural fluid. *Diagn Cytopathol* 1998; **18**:453–457.

6 Kodama K, Doi O, Higashiyama M, Horai T, Tateishi R, Nakagawa H. Primary and metastatic pulmonary meningioma. *Cancer* 1991; **67**:1412–1417.

7 Williamson BE, Stanton CA, Levine EA. Chest wall metastasis from recurrent meningioma. *Am Surg* 2001; **67**:966–968.

8 Gabizon AA. Pegylated liposomal Doxorubicin: metamorphosis of an old drug into a new form of chemotherapy. *Cancer Invest* 2001; **19**:424–436.

9 Koukourakis MI, Koukouraki S, Fezoulidis I, Kelekis N, Kyrias G, Archimandritis S, *et al.* High intratumoural accumulation of stealth liposomal doxorubicin (Caelyx) in glioblastomas and in metastatic brain tumours. *Br J Cancer* 2000; **83**:1281–1286.

10 Fabel K, Dietrich J, Hau P, Wismeth C, Winner B, Przywara S, *et al.* Long-term stabilization in patients with malignant glioma after treatment with liposomal doxorubicin. *Cancer* 2001; **92**:1936–1942.

11 Siegal T, Horowitz A, Gabizon A. Doxorubicin encapsulated in sterically stabilized liposomes for the treatment of a brain tumor model: biodistribution and therapeutic efficacy. *J Neurosurg* 1995; **83**:1029–1037.

12 Lyass O, Uziely B, Ben-Yosef R, Tzemach D, Heshing NI, Lotem M, *et al.* Correlation of toxicity with pharmacokinetics of pegylated liposomal doxorubicin (Doxil) in metastatic breast carcinoma. *Cancer* 2000; **89**:1037–1047.

13 Colbern GT, Steinmetz K, Bandak S, Johnson LG, Musterer RS, Hiller AG, *et al.* Amifostine reduces severity and incidence of Doxil-induced palmar/plantar erythrodysesthesia in rats but does not reduce Doxil antitumor efficacy or alter pharmacokinetics in mice. *Proc Am Soc Clin Oncol* 2000; **19**:abstr 815.

14 Christov C, Lechapt-Zalpman E, Adle-Biassette H, Nachev S, Gherardi RK. Vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) and its receptor flt-1 in microcystic meningiomas. *Acta Neuropathol* 1999; **98**:414–420.

15 Harrington KJ, Mohammadtaghi S, Uster PS, Glass D, Peters AM, Vile RG, *et al.* Effective targeting of solid tumors in patients with locally advanced cancers by radiolabeled pegylated liposomes. *Clin Cancer Res* 2001; **7**:243–254.

16 Gabizon A, Catane R, Uziely B, Kaufman B, Safra T, Cohen R, *et al.* Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. *Cancer Res* 1994; **54**:987–992.