Successful treatment of a pineal endodermal sinus tumor

Case report

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A patient with a pineal endodermal sinus tumor is presented who was successfully treated by a combination of surgery, adjuvant chemotherapy, and craniospinal irradiation. Two years after diagnosis, he is free of any disease. A review of the literature shows that such an outcome is very unusual. A multidisciplinary treatment is recommended for this rare tumor, using chemotherapy as adjuvant treatment.

Key Words • pineal endodermal sinus • tumor • alpha-fetoprotein • chemotherapy • radiotherapy

Endodermal sinus tumors or yolk sac tumors are rare cancers of the germ-cell-derived extraembryonic tissues. Like other cancers of germinocytic origin, they arise in midline sites such as the gonads, sacrococcygeal area, retroperitoneum, mediastinum, suprasellar region, and pineal gland. Intracranial endodermal sinus tumors represent 7% of primary intracranial germinal cancers, which themselves represent only 0.4% to 3.5% of primary intracranial neoplasms in Western countries. Histologically, 50% of pineal gland endodermal sinus tumors are mixed and contain various proportions of other germ-cell elements including germinoma, teratoma, embryonal-cell carcinoma, and choriocarcinoma. Most pineal endodermal sinus tumors synthesize alpha-fetoprotein, and this marker, measured in serum and cerebrospinal fluid (CSF), may be useful for diagnosis and to assess responsiveness to treatment. Endodermal sinus tumors of the pineal gland are highly aggressive neoplasms and the survival rate is poor.

We describe a case of long-term complete remission of a pineal gland endodermal sinus tumor treated by a combination of surgery, cytotoxic chemotherapy, and radiotherapy. We review the other reported cases and stress the importance of a combined therapeutic approach in the management of this rare tumor.

Case Report

This 14-year-old boy with unremarkable medical history first presented in April, 1988, with intermittent frontal headaches beginning 2 months before. He suffered diplopia, nausea, vomiting, and drowsiness.

Examination. There was an absence of upward gaze and poor ocular convergence. Fundoscopic examination disclosed papilledema without hemorrhage. No other neurological deficit was noted apart from mild ataxia. Computerized tomography revealed a pineal tumor and marked hydrocephalus (Fig. 1a). Serum alpha-fetoprotein and human chorionic gonadotropin (HCG) levels were raised at 1050 kU/liter (normal ≤ 10 kU/liter) and 151 IU/liter (normal ≤ 4 IU/liter), respectively.

Operation. Right occipital craniotomy with transcortical microsurgical excision of the lesion was performed in May, 1988. The excision appeared grossly complete (Fig. 1b right). Histological examination showed a malignant endodermal sinus tumor (yolk sac tumor) with a high mitotic rate and pathognomonic Schiller-Duval bodies (Fig. 2). There was also an element of mature teratoma comprising keratinizing epithelium, smooth muscle, and endocrine-type cells.

Postoperative Course. After surgery, the hydrocephalus resolved but upward vision was still limited and diplopia on right lateral gaze persisted. The serum HCG content fell to less than 2 IU/liter but, after an initial impressive drop to 49 kU/liter, the alpha-fetoprotein level rose to 88 and 113 kU/liter 18 and 25 days, respectively, after surgery (Fig. 3). Alpha-fetoprotein but not HCG levels were also elevated in the CSF.
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(97 kU/liter). Cytological examination of the CSF for tumor cells was negative and remained so on later lumbar punctures.

Faced with the dismal prognosis, it was elected to treat the patient with chemotherapy according to the POMB-ACE regimen for anaplastic germ-cell tumors. This intensive regimen comprises an initial period of intravenous platinum (P), vincristine (O), methotrexate (M), and bleomycin (B) followed after a 10-day hiatus by actinomycin D (A), cyclophosphamide (C), and etoposide (E). This regimen was chosen because of a previous report of its efficacy in several cases of nonseminomatous germ-cell tumors metastatic to the brain. The first cycle of POMB was begun on the 18th postoperative day. It consisted of intravenous vincristine, 1 mg/sq m, and methotrexate, 300 mg/sq m on Day 1; bleomycin, 15 mg, on Days 2 and 3; and cisplatin, 120 mg/sq m, on Day 4. At the same time the patient was given 10 mg methotrexate intrathecally. After the POMB treatment, alpha-fetoprotein levels were still elevated in serum (67 kU/liter) and CSF (34 kU/liter).

The patient was readmitted to the hospital 10 days later to receive a 3-day course of etoposide (VP-16, 100 mg/sq m on Days 1 to 3), actinomycin D (0.5 mg on Days 2 and 3), and cyclophosphamide (500 mg/sq m on Day 3), as well as a second dose of intrathecal methotrexate (10 mg). The serum and CSF alpha-feto-

FIG. 1. Left: Preoperative computerized tomography (CT) scans showing the enhancing tumor in the region of the pineal gland. Right: Postoperative CT scan confirming the macroscopically complete resection of tumor with consequent relief of hydrocephalus.

FIG. 2. Photomicrograph of the tumor specimen showing the typical appearance of an endodermal sinus tumor with large vacuolated cells and prominent nucleoli. In the center a pathognomonic Schiller-Duval body, a glomeruloid structure with surrounding crescentic space, can be seen. H & E, × 200.

FIG. 3. Plot of serum alpha-fetoprotein (AFP) level during and following treatment. The theoretical decay curve assumes a biological half-life of 5 days following a total extirpation of the tumor. For definitions of POMB and ACE chemotherapy see text; R/T = radiation therapy.
protein levels eventually fell to normal 2 weeks later (Fig. 3). A second course of POMB was given but the dose of cisplatin was reduced to 100 mg because of intense nausea and vomiting during the first course and a transient rise in creatinine and urea. A second course of ACE, together with a third dose of 10 mg methotrexate intrathecally, was then given.

Finally, it was decided to consolidate the treatment with craniospinal irradiation 3 weeks after the completion of chemotherapy. The whole brain received 2880 cGy in 16 fractions over a 3-week period with a subsequent boost to the third ventricle area, to a final tumor dose of 5400 cGy in 30 fractions over 46 days using a three-field technique. Spinal irradiation (2550 cGy in 17 fractions over 25 days) completed this treatment.

Over the next year, improvement was noted in the patient’s ocular movements; in particular, good upgaze was restored. Currently, 24 months after the diagnosis the patient is still clinically, biologically, and radiologically free of any disease. His pupils still react sluggishly to light and briskly to accommodation. Of note, his pituitary function is normal and his scholastic performance remains unchanged.

Discussion

Pineal endodermal sinus tumor is a very rare but highly aggressive nonseminomatous germ-cell neo-plasm. Of the 29 patients reported in the literature (Tables 1 and 2), 24 were dead by 14 months after the diagnosis.

The results of surgery and/or radiotherapy without chemotherapy are very disappointing (Table 1). Only two of 21 patients survived at 6.5 months and 3.5 years. Both underwent partial resection followed by craniospinal irradiation. The surgical procedure was limited to a biopsy and/or insertion of a shunt for the majority of patients. In the earlier literature, surgery for pineal tumors carried an unacceptably high mortality rate but, with modern techniques, resection can be counternanced. The commoner germinomas of the pineal region are radiosensitive and patients are often cured by shunt placement and a therapeutic trial of radiation, but it is clear that such an approach cannot be relied upon to cure the rare patient with an endodermal sinus tumor. As shown in Table 1, no such tumor has been cured by radiotherapy alone.

The emergence of extremely effective chemotherapy for gonadal and extragonadial germ-cell tumors has changed management concepts of intracranial germ-cell tumors. Protocols using synergistic cytotoxic agents, including vinblastine, vincristine, actinomycin D, bleomycin, Adriamycin, cyclophosphamide, and cisplatin, have achieved complete remission rates of 60% to 90% against localized and metastatic gonadal and extrago-
Pineal endodermal sinus tumor

### TABLE 2
Reported cases of pineal endodermal sinus tumors treated with chemotherapy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Authors &amp; Year</th>
<th>Histology*</th>
<th>Surgery†</th>
<th>Radiotherapy</th>
<th>Chemotherapy‡</th>
<th>Outcome, Survival Time Since Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prioleau &amp; Wilson, 1976</td>
<td>pure</td>
<td>S &amp; PR</td>
<td>yes</td>
<td>adjuvant: VAC</td>
<td>alive, &gt; 13 yrs</td>
</tr>
<tr>
<td>2</td>
<td>Edwards, et al., 1988</td>
<td>mixed (Ch)</td>
<td>S</td>
<td>yes</td>
<td>adjuvant: PCB, VCR</td>
<td>died, 9 mos</td>
</tr>
<tr>
<td>3</td>
<td>Stachura &amp; Mendelow, 1980</td>
<td>pure</td>
<td>S</td>
<td>yes</td>
<td>recurrent tumor: BCNU</td>
<td>died, 13 mos</td>
</tr>
<tr>
<td>4</td>
<td>Arita, et al., 1980</td>
<td>pure</td>
<td>S</td>
<td>yes</td>
<td>1st recurrence: MTX</td>
<td>died, 13 mos</td>
</tr>
<tr>
<td>5</td>
<td>Otsen, et al., 1982</td>
<td>pure</td>
<td>S &amp; PR</td>
<td>yes</td>
<td>2nd recurrence: VCR, bleomycin</td>
<td>died, 22 mos</td>
</tr>
<tr>
<td>6</td>
<td>Anderson, 1987</td>
<td>pure</td>
<td>no</td>
<td>yes</td>
<td>abdominal metastasis: VAC</td>
<td>died, 12 mos</td>
</tr>
<tr>
<td>7</td>
<td>Allen, et al., 1987</td>
<td>pure (parietal)</td>
<td>B or PR</td>
<td>yes</td>
<td>recurrent tumor: bleomycin, VCR, VP-16, CP</td>
<td>alive, &gt; 12 mos</td>
</tr>
<tr>
<td>8</td>
<td>Edwards, et al., 1988</td>
<td>mixed (T)</td>
<td>PR</td>
<td>yes</td>
<td>adjuvant: CP, VCR, MTX, bleomycin, VP-16, actin-D, cyclo</td>
<td>alive, &gt; 24 mos</td>
</tr>
</tbody>
</table>

* Nonendodermal sinus tumor component of the tumors: Ch = choriocarcinoma; T = teratoma.
† S = shunt; PR = partial removal; B = biopsy; + = surgery but no details available.
‡ VAC = vincristine (VCR) + actinomycin D (Actino D) + cyclophosphamide (cyclo); PCB = procarbazine; MTX = methotrexate; bleo = bleomycin; VCB = vindesine + cisplatin + bleomycin; VAB = vindesine + bleomycin + cisplatin + cyclophosphamide; VP-16 = etoposide; CP = cyclophosphamide.

Nodular nonsemionomatous germ-cell tumors in combination with surgery and irradiation. Several complete responses to chemotherapy have also been reported in germ-cell brain metastases. Moreover, in a review of 81 cases of primary intracranial nonseminomatous germ-cell tumors, Graziano, et al., found nine long-term survivors, eight after chemotherapy and radiotherapy and only one after radiotherapy as the primary modality.

We found only eight cases of pineal endodermal sinus tumor treated by chemotherapy (Table 2). Five patients who died received chemotherapy only when the tumor was known to have recurred or metastasized. Two of three patients who received adjuvant chemotherapy were alive 13 years and 12 months after diagnosis. In the third adjuvant patient, there was an initial complete response after radiotherapy and chemotherapy, but the patient died 9 months later with local recurrence and seeding to the spine and peritoneum. Metastatic spread through the CSF and ventriculoperitoneal shunts is a well-documented risk in pineal endodermal sinus tumors. Our patient, alive 2 years after diagnosis, was treated with adjuvant chemotherapy following a macroscopically complete resection of the tumor. The serum alpha-fetoprotein levels (Fig. 3) fell initially and then rose, strongly suggesting that there was a microscopic residuum of tumor. The subsequent decrease to normal levels after the first round of POMB-ACE chemotherapy was an invaluable measure, and gave us the confidence to administer only one further course of POMB-ACE rather than an arbitrary (larger) number of cycles.

The decision to consolidate with craniospinal irradiation was not based on hard evidence, but influenced by anecdotal reports of patients with pineal tumor relapsing after an initial response to chemotherapy when radiotherapy was omitted. Radiotherapy with careful fractionation tailored to the doses used seemed to be an acceptable risk and in the event was well tolerated. There appeared to be no logic in omitting the spinal field in view of the high rate of CSF seeding described with pineal endodermal sinus tumors.

### Conclusions
We report the third case of long-term survival among patients with pineal endodermal sinus tumors managed with chemotherapy as adjuvant treatment. We stress a multidisciplinary approach to pineal endodermal sinus tumors based on combined surgery, chemotherapy, and radiotherapy. Surgery allows a definite diagnosis and removes most of the tumor mass. Combination chemotherapy using a platinum-based regimen must be given as adjuvant treatment without delay. Radiotherapy (whole neuraxis irradiation) can be used to complete the treatment. The response to therapy should be monitored by serial determinations of tumor markers.

### References


31. von Martin H, Vogel S: [Malignant stem cell tumor of the pineal region with unusual differentiation.] Zentralbl Allg Pathol 120:391-397, 1976 (Ger)


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