Mixed germ-cell tumor of the pineal region

Case report

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The case is presented of a 15-year-old boy with a mixed nongerminomatous germ-cell tumor of the pineal region associated with elevated cerebrospinal fluid and serum levels of the beta subunit of human chorionic gonadotropin. Treatment consisted of initial subtotal resection followed by radiotherapy and systemic chemotherapy with cisplatin, vinblastine, and bleomycin. The patient is alive without evidence of tumor 37 months after his initial diagnosis. A literature review of intracranial embryonal carcinoma and choriocarcinoma provided the rationale for a combined-modality approach to this otherwise lethal neoplasm.

KEY WORDS • pineal tumor • brain neoplasm • embryonal carcinoma

Tumors of the pineal region account for 0.4% to 1.0% of all intracranial neoplasms in the United States and Europe and 4% in Japan. Tumors arising in this area include pineal parenchymal tumors (pineoblastoma and pineocytoma), germ-cell tumors (germinoma, mature teratoma and teratocarcinoma, embryonal carcinoma, yolk-sac tumor, and choriocarcinoma), glial tumors, and cysts. Germ-cell tumors are considered to account for more than 50% of tumors in this region and appear to be analogous to tumors arising in the testis, ovary, sacrococcygeal region, retroperitoneum, and anterior mediastinum.

Initial management of pineal region tumors represents an area of controversy. Surgical exploration of the pineal region has historically been associated with a high mortality rate. Since approximately 70% of these tumors are benign or radiosensitive, the most common mode of therapy has been ventriculoperitoneal shunting and radiotherapy. More recently, however, improvements in neurosurgical technique have decreased surgical mortality to less than 5%. This has encouraged the taking of an initial biopsy to establish histopathological diagnosis so as to direct specific therapy. While shunting and radiotherapy yield 60% to 70% 5-year survival rates in germinomas, this approach is clearly inadequate for nongerminomatous tumors such as embryonal carcinoma, teratocarcinoma, choriocarcinoma, and yolk-sac (endodermal sinus) tumors. These tumors carry a grave prognosis with a primary radiotherapeutic approach.

We report the successful treatment of a 15-year-old boy with embryonal carcinoma of the pineal region. He underwent initial exploration and subtotal resection, and received postoperative radiotherapy and combination chemotherapy with cisplatin, vinblastine, and bleomycin.

Case Report

This 15-year-old male high-school student was admitted to our institution in December, 1982, for evaluation of the sudden onset of severe frontal headache, blurred vision, and nausea and vomiting.

Examination. Physical examination disclosed Pari- naud's syndrome (upward-gaze paralysis, sluggish pupillary response to light, and contraction nystagmus), decreased visual acuity (20/50 bilaterally), and anterior mediastinum. A computerized tomography (CT) scan showed hemorrhage in the region of the pineal gland with possible hydrocephalus (Fig. 1). An angiogram revealed a small area of increased vascularity just posterior to the lateral posterior choroidal vessels with early appearance of the internal cerebral vein, suggesting a
Pineal germ-cell tumor

**FIG. 1.** Left: Computerized tomography (CT) scan with enhancement at initial presentation. There is a discrete area of increased density in the pineal region at the posterior aspect of the third ventricle. The lateral and third ventricles are slightly prominent. No significant contrast enhancement was noted. Right: CT scan obtained shortly after two grand mal seizures showing extensive edema of the white matter involving the right temporal and parietal regions. There is minimal mass effect and the prominent calcified pineal mass is unchanged from the prior posttreatment CT scan. These findings are most consistent with radiation changes.

small arteriovenous malformation and recent hemorrhage. A repeat arteriogram and CT scan were obtained 3 weeks later. A vascular lesion in the pineal region consistent with tumor or arteriovenous malformation was observed. There was almost complete resolution of the hematoma seen previously. An Amipaque (metrizamide) cisternogram showed a nonfilling defect in the pineal area compatible with tumor or clot from previous hemorrhage. Lumbar puncture revealed a cerebrospinal fluid (CSF) glucose level of 50 mg/dl, a protein concentration of 37 mg/dl, 4 white blood cells per high-power field (100% mononuclear cells), and 10 red blood cells per high-power field. Cultures and cytological studies of the CSF were negative.

**Operation.** A craniotomy was performed on February 10, 1983, with subtotal excision of a pineal tumor through a supracerebellar infratentorial approach. Residual cystic tumor was seen infiltrating into the left thalamus. The tumor was a malignant germ-cell tumor, consistent with embryonal carcinoma and with possible choriocarcinomatous elements (Fig. 2). Further evaluation, including careful genitourinary physical examination, CT of the chest and abdomen, and routine laboratory studies, was unremarkable except for elevation of the human chorionic gonadotropin beta subunit (β-HCG) in the CSF and serum, with levels of 3060 and 524 mIU/ml, respectively. Alpha-fetoprotein and carcinoembryonic antigen studies were negative in both CSF and serum.

**Postoperative Course.** Radiotherapy was begun 2 weeks postoperatively with the delivery of 4000 cGy in 20 fractions to the ventricular system. The field was then reduced to the pineal region and an additional 1600 cGy was administered in a total of 5 weeks of therapy. At the completion of radiotherapy, both CSF and serum β-HCG values were normal (Fig. 3). Because of the poor prognosis associated with radiotherapy alone, combined chemotherapy was initiated 10 weeks after surgery, consisting of cisplatin (20 mg/sq m daily

**FIG. 2.** Photomicrograph showing a representative field of the tumor composed of masses of nearly uniform large cells resembling cytotrophoblasts with pale cytoplasm, relatively large nuclei, prominent nucleoli, and mitoses. These masses are surrounded by flattened cells with very darkly stained nuclei, ill-defined borders, and variable amounts of cytoplasm, suggesting a syncytiotrophoblastic nature (arrows). H & E, × 110.

**FIG. 3.** Graph showing serial serum and cerebrospinal fluid (CSF) levels of human chorionic gonadotropin beta subunit (β-HCG) in relation to treatment consisting of surgery, radiotherapy, and chemotherapy. Velban = vinblastine.
for 5 days), vinblastine (0.15 mg/kg on Days 1 and 2), and bleomycin (30 units weekly to a total of 360 units)\textsuperscript{16,17} (Fig. 3). Five courses of therapy were given every 3 to 4 weeks with saline diuresis and anti-emetics.

Four months after the completion of chemotherapy the patient had two grand mal seizures. A CT scan showed extensive edema of the white matter involving the right temporal and parietal lobes compatible with radiation changes (Fig. 1 right). The pineal region was unchanged. Electroencephalography revealed a focus of seizure activity in the right temporal and occipital areas. The CSF and serum \(\beta\)-HCG levels remained normal. Diphenylhydantoin and phenobarbital were given, and a follow-up CT scan performed 7 months later showed resolution of edema. The patient has successfully completed high school, having participated in cross-country running. At 37 months after his initial diagnosis, his development and intellectual capacity appear normal and no further seizure activity has occurred.

### Discussion

While intracranial germinomas are generally radioresponsive, with 5-year survival rates of 50% to 80%, the results of the primary radiotherapeutic approach to therapy of nongerminomatous germ-cell tumors of this region have been dismal. Recent reviews of intracranial embryonal carcinoma (including yolk-sac tumor) by Eberts and Ransburg,\textsuperscript{14} Packer, et al.,\textsuperscript{37} and others indicate only three long-term survivors among 45 well-documented cases; these patients were reported to be alive 1, 5,\textsuperscript{3} and 7 years after diagnosis.\textsuperscript{2-7,21-33,35,36,40-43,45-49,52,55,56,60} Two of these three patients were treated with radiotherapy and chemotherapy consisting of vincristine, actinomycin-D, and cyclophosphamide,\textsuperscript{37,40} and the third received radiotherapy alone.\textsuperscript{8} Most patients died of postoperative complications or of local recurrence within 1 year of diagnosis.

In 1984, Chan, et al.,\textsuperscript{3} reviewed 35 cases of primary intracranial choriocarcinoma and reported five survivors alive 18 to 48 months after diagnosis.\textsuperscript{19,27,58} All long-term survivors were treated with a combination of initial resection or biopsy, radiotherapy, and chemotherapy. Chemotherapy was varied but included drugs active against germ-cell tumors such as vinblastine, bleomycin, cisplatin, 4’-dimethylamino-2,6-di(thiophenyl)pyridine 9-(4,6-0-ethylidene-B-D-glucopyranoside)(VP-16), cyclophosphamide, actinomycin-D, doxorubicin, and methotrexate (systemic and intrathecal). One patient, after initial relapse, was salvaged with a combination of vinblastine, bleomycin, cisplatin, and doxorubicin.\textsuperscript{58} Allen, et al.,\textsuperscript{3} reported an additional patient alive at 2 years after treatment with radiotherapy plus chemotherapy with high-dose methotrexate and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). Thus, of the 81 reported cases of intracranial embryonal endodermal sinus tumor and choriocarcinoma, there was only one long-term survivor who was treated with radiotherapy as the primary modality. The other eight long-term survivors received multimodality therapy consisting of surgery, radiotherapy, and chemotherapy.

Our present case represents successful treatment with initial subtotal surgical resection, radiotherapy, and intensive combination chemotherapy. An interesting feature of this case was the elevated serum and CSF levels of \(\beta\)-HCG. This marker is usually associated with choriocarcinomatous elements, less frequently with embryonal carcinoma,\textsuperscript{3} and rarely with syncytiotrophoblastic differentiation in germinomas.\textsuperscript{29} In our case, the elevated \(\beta\)-HCG most likely represented a choriocarcinomatous component of the tumor. The primary issue in our patient's management was the use of systemic chemotherapy, even though serum and CSF levels of \(\beta\)-HCG had normalized with their predicted half-lives immediately after radiotherapy. Because of the grave prognosis of these lesions treated with surgery and radiation alone, we considered that additional therapy was warranted, particularly since response to chemotherapy in patients with recurrent disease has been rare.\textsuperscript{58} The regimen described by Einhorn, et al.,\textsuperscript{15,20} was chosen because of its success in the treatment of adult testicular carcinoma and extragonadal germ-cell tumors. In addition, dramatic responses to cisplatin, bleomycin, and vinblastine have been reported with recurrent germinomas.\textsuperscript{28,34} Acceptable levels of bleomycin and cisplatin in the CSF of a patient treated for recurrent germinoma with cisplatin, bleomycin, and vinblastine have also been shown.\textsuperscript{18} While experience with this regimen in children is limited, it may offer an advantage over delivery of actinomycin-D which is known to enhance radiation toxicity.\textsuperscript{31,58} In our case, the patient had two grand mal seizures in conjunction with a dramatic abnormality on the CT scan obtained 8 months after the completion of radiotherapy. It is possible that this represented an interaction between drugs and radiotherapy, since bleomycin can enhance toxicity to normal tissues\textsuperscript{13} and cisplatin is a radiation potentiator.\textsuperscript{13}

Rrelapse after 2 years from diagnosis is uncommon in gem-cell neoplasms at other sites.\textsuperscript{15} The natural history of nongerminomatous germ-cell tumors appears to be similar, with most recurrences occurring within 1 year. Packer, et al.,\textsuperscript{38} reports the recurrence of a pineal chorionicarcinoma 2 years after treatment, but this appears to be the exception. Thus, the chance for cure in our patient is excellent. Since nongerminomatous germ-cell tumors of the pineal region are rare, the optimal approach is not established at this time. The combination of initial surgical exploration with biopsy, radiotherapy, and systemic chemotherapy and the monitoring of serum and CSF levels may provide the optimal approach to these lethal neoplasms.

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S. L. Graziano, et al.
Pineal germ-cell tumor

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303

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