Review Article

Intracranial germ-cell tumors: natural history and pathogenesis

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The natural history of primary intracranial germ-cell tumors (GCT's) is defined from 389 previously published cases, of which 65% were germinomas, 18% teratomas, 5% embryonal carcinomas, 7% endodermal sinus tumors, and 5% choriocarcinomas. Intracranial GCT's display specificity in site of origin. Ninety-five percent arise along the midline from the suprasellar cistern (37%) to the pineal gland (48%), and an additional 6% involve both sites. The majority of germinomas (57%) arise in the suprasellar cistern, while most nongerminomatous GCT's (68%) preferentially involve the pineal gland (p < 0.0001). The age distribution of afflicted patients is unimodal, centering with an abrupt surge in frequency in the early pubertal years; 68% of patients are diagnosed between 10 and 21 years of age. Nongerminomatous GCT's demonstrate an earlier age of onset than do germinomas (p < 0.0001). Prolonged symptomatic intervals prior to diagnosis are common in germinomas (p = 0.0007), in suprasellar GCT's (p = 0.001), and among females (p = 0.02). Parasellar germinomas commonly present with diabetes insipidus, visual field defects, and hypothalamic-pituitary failure. Nongerminomatous GCT's present as posterior third ventricular masses with hydrocephalus and midbrain compression. Germ-cell tumors may infiltrate the hypothalamus (11%), or disseminate to involve the third ventricle (22%) and spinal cord (10%). Among a subpopulation of 263 conventionally treated patients, two factors were of prognostic significance: 1) histological diagnosis; germinomas were associated with significantly longer survival than nongerminomatous GCT's (p < 0.0001); and 2) staging of the extent of disease; this emphasizes the ominous character of involvement of the hypothalamus (p = 0.0002), third ventricle (p = 0.02), or spinal cord (p = 0.01). Specific recommendations regarding the necessity of histological diagnosis and staging of the extent of disease are made in light of modern chemotherapeutic advances.

The pathogenesis of GCT's may be revealed by their specificity of origin within the positive (suprasellar cistern-suprachiasmatic nucleus) and negative (pineal) regulatory centers for gonadotropin secretion within the diencephalon. The abrupt rise in age distribution at 10 to 12 years suggests that the neuroendocrine events of puberty are an "activating" influence in the malignant expression of these embryonal tumors.

KEY WORDS • germ-cell tumor • germinoma • teratoma • choriocarcinoma • embryonal carcinoma • endodermal sinus tumor • natural history • prognosis

Despite recent reviews, pineal and third ventricular tumors remain a perplexing clinical problem due to the diverse hamartomatous and malignant entities that may occur in this area. Further confusion stems from lack of familiarity with the unique biological attributes of primary diencephalic-epiphyseal germ-cell neoplasms. These differ substantially in natural history from tumors of pineal parenchymal and glial origin.

Introduction

Tumors of germ-cell derivation comprise five interrelated neoplasms which demonstrate a hierarchical order of increasing malignant behavior: germinoma, teratoma (including immature and malignant types), embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma. Each represents the malignant correlate of a normal embryonic stage of development: the primordial germ cell (germinoma), the embryonic differentiated derivative (teratoma) of the pluripotential stem cell of the embryo proper (embryonal carcinoma), as well as the extraembryonic differentiated derivatives which form the yolk sac endoderm (endodermal sinus tumor) and trophoblast (choriocarcinoma). The cancers of germinal origin arise in specific midline sites: the gonads, sacrococcygeum, retroperitoneum, medias-
TABLE 1
Clinical and histological features of human germ-cell tumors analyzed by site of origin*

<table>
<thead>
<tr>
<th>Site of Origin</th>
<th>Peak Age of Occurrence</th>
<th>Sex Ratio (M:F)</th>
<th>Predominant Histological Pattern of Malignancy</th>
<th>Mixed Histological Pattern (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>testis</td>
<td>0-3 2-5 15-30 31+</td>
<td>1:0 EST, TE</td>
<td>63% EST, TE, 60% EC, TE</td>
<td>36% NA 40% NA</td>
<td>19, 20, 45, 56, 88, 89</td>
</tr>
<tr>
<td>ovary</td>
<td>10-29 80 11-20 30</td>
<td>0:1 benign TE</td>
<td>60-80 EST, TE</td>
<td>NA</td>
<td>19, 76, 121, 144</td>
</tr>
<tr>
<td>sacrococcygeum</td>
<td>0-3 95+</td>
<td>1:3 benign TE</td>
<td>56-82 EST, TE</td>
<td>NA</td>
<td>4, 19, 26, 44, 83, 138</td>
</tr>
<tr>
<td>retroperitoneum</td>
<td>0-3 33 11-20 30</td>
<td>2:1 benign TE</td>
<td>NA</td>
<td>NA</td>
<td>19, 33, 96</td>
</tr>
<tr>
<td>diencephalon</td>
<td>15-35 80+ 10-21 68</td>
<td>4-11:1 benign TE</td>
<td>46-67 EC, TE</td>
<td>38% 30% 86% 95%</td>
<td></td>
</tr>
</tbody>
</table>

* Abbreviations: GE = germinoma; TE = teratoma; EC = embryonal carcinoma; EST = endodermal sinus tumor; NA = not available.

This retrospective review allows us to present key features of the natural history of this tumor type and its major prognostic determinants. These principles will be discussed in terms of their impact on the stratification of high-risk populations, current therapeutic options, and future avenues of investigation.

Clinical Material and Methods

Of 711 cases of diencephalic and pineal tumors reviewed in 119 published reports, pathological examination confirmed the diagnosis of primary intracranial GCT in 389 clinically informative cases. These cases form the basis for this review.

Natural History

The natural history of 389 retrospectively analyzed primary GCT’s of the CNS was established. This population included 253 germinomas (65%), 70 teratomas (18%), 21 embryonal carcinomas (5%), 26 endodermal sinus tumors (7%), and 19 choriocarcinomas (5%). The pathological diagnosis was provided by a precise histological description or accompanying photograph. Among larger series, the specified germinal origin of the tumor was accepted. The GCT classification employed was modified from that of the Intergroup Testicular Protocol and the World Health Organization. In this modification, the subtypes include (in order of increasing malignancy): germinoma, teratoma, embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma.

Further insight into the pathogenesis of germinal neoplasms may be gained by their apparent relationship with the neuroendocrine regulatory centers of the diencephalon. Primary intracranial GCT’s are rare in North America. We have, therefore, reviewed cases reported in the English language between 1950 and 1981, in which pathological examination confirmed the diagnosis of a primary GCT of the central nervous system (CNS). This interval was chosen because, after 1950, consensus existed on the concept of the germinal cell derivation of germinoma, teratoma, embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma. This retrospective review allows us to present key features of the natural history of this tumor type and its major prognostic determinants. These principles will be discussed in terms of their impact on the stratification of high-risk populations, current therapeutic options, and future avenues of investigation.

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J. Neurosurg. / Volume 63 / August, 1985
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to be of germinal cell origin, such as pineoblastomas, pineocytomas, epidermoid tumors, dermoid tumors, primitive neuroectodermal tumors, and hamartomas, are outside the scope of this report. Excluded from study were cases in which the diagnosis was made only post mortem, and those with incorrectly identified, unstated, or poorly specified (such as "pinealoma") histology. The only exception was the inclusion of the germinomas identified by Sano and Matsunari\(^1\) as the "two-cell pattern of pinealoma."

The site of tumor origin was identified from clinical, roentgenological, surgical, and pathological descriptions. The "age at diagnosis" was defined as the patient's age at the date of diagnosis. Pre- and postdiagnostic intervals were calculated from this date. All reports were analyzed twice to ensure uniformity and accuracy. Cases reported in more than one publication were counted only once.

**Multivariant Analysis of the Prognostic Determinants**

Multivariant analysis of a subpopulation was undertaken so as to determine which major clinical and histological features correlated with prognosis among conventionally treated patients. In order to control for the effect of differing therapies upon survival we excluded: 1) five patients who received no treatment despite a diagnosis of an intracranial tumor; 2) one patient for whom the therapy was not stated; 3) 30 patients treated by surgery alone; 4) 19 patients treated by surgery and chemotherapy; and 5) 71 patients in whom the duration of survival was unknown. Thus, this subpopulation for survival analysis consisted of 263 patients harboring the following tumors: 189 germinomas (72%), 35 teratomas (13%), 14 embryonal carcinomas (5%), 15 endodermal sinus tumors (6%), and 10 choriocarcinomas (4%). Despite the difference in sample size, the natural history population of 389 patients and the survival analysis population of 263 patients were alike for distribution by histological diagnosis, site of tumor origin, extent of dissemination, sex, and age at diagnosis (data not presented). Differences in percentages and distributions were analyzed with a chi-squared test.\(^6^6\) A step-down procedure was used on Cox proportional hazards models to identify the patient characteristics most strongly correlated with survival time.\(^3^9\) Plots of survival curves were made using the modified Kaplan-Meier procedure.\(^6^6\)

**Results**

**Natural History Study**

**Tumor Origin.** Table 2 presents the sites of origin of the GCT's in this series. Ninety-five percent of primary intracranial GCT's originated in the region of the third ventricle along an axis from the suprasellar cistern (37%) to the pineal gland (48%). Involvement of both sites, either sequentially or simultaneously, occurred rarely (6%), as did origin within the third ventricle (3%), basal ganglia-thalamus (3%), or other ventricular sites (3%).

Distinctions existing between germinomas and nongerminomatous GCT's will be emphasized hereafter. Germinomas preferentially (57%, including patients with multicentric involvement) involved the suprasellar region, while 68% of nongerminomatous GCT's arose in the pineal gland (p < 0.0001). The GCT's arising within the basal ganglia-thalamus were all germinomas,\(^2^4,6^9,7^2,1^2^9\) whereas those in the lateral ventricular-cerebellar region,\(^6^9,6^6,7^7,1^3^1\) or the fourth ventricular-cerebellar region,\(^9,1^2^7\) or those that appeared holocranial\(^1^3^1\) were nongerminomatous GCT's.

**Correlation of Gender and Age at Diagnosis.** The series included 269 males and 120 females, for a ratio of 2.24:1 (Table 2). This ratio increased for nongerminomatous GCT's (3.25:1) in contrast to germinomas (1.88:1) (p = 0.01). Germ-cell tumors were found in the suprasellar region in 75% of female patients; in males, pineal involvement was more frequent (67%) (p = 0.0001). The age distribution of patients with GCT of the CNS ranged from newborn to 69 years. The peak occurrence for both sexes was in the 10- to 12-year-old group, with 68% of patients diagnosed between 10 and 21 years of age (Fig. 1). Nongerminomatous GCT's (24%, Fig. 2) were more frequently diagnosed between birth and 9 years than were germinomas (11%, Fig. 3) (p < 0.0001). Childhood presentation was common for teratomas (31%) and choriocarcinomas (36%).

**Correlation of Symptomatic Interval Prior to Diagnosis and Presenting Signs and Symptoms.** The duration of symptoms prior to diagnosis was known in 215 patients (52% of those with germinomas and 62% of those with nongerminomatous GCT's). Of patients with germinomas, 35% were reported to be symptomatic for 6 months or longer, half of these in excess of

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**Table 2** Sites of origin and dissemination of 389 GCT's related to histology and patient's sex

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Germinoma M</th>
<th>NG-GCT M</th>
<th>Sex F</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>suprasellar</td>
<td>49</td>
<td>18</td>
<td>23</td>
<td>69</td>
</tr>
<tr>
<td>pineal gland</td>
<td>38</td>
<td>65</td>
<td>61</td>
<td>19</td>
</tr>
<tr>
<td>both</td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>other</td>
<td>5</td>
<td>14</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>secondary sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypothalamus</td>
<td>10</td>
<td>15</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>3rd ventricle</td>
<td>16</td>
<td>31</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>spinal cord</td>
<td>11</td>
<td>7</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>systemic</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>peritoneum</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>elsewhere in CNS</td>
<td>11</td>
<td>23</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>

* Abbreviations: GCT = germ-cell tumor; NG = nongerminomatous; CNS = central nervous system.
† Other sites of origin include the third ventricle, basal ganglia-thalamus, lateral and fourth ventricles, and holocranial GCT.

FIG. 2. Distribution by age at diagnosis for patients with intracranial teratoma (upper left), embryonal carcinoma (upper right), endodermal sinus tumor (lower left), and choriocarcinoma (lower right). Cong'l = congenital. (Reproduced with permission from Jennings MT, Gelman R, Hochberg F: Intracranial germ cell tumors: natural history and pathogenesis, in Neuwelt EA (ed): Diagnosis and Treatment of Pineal Region Tumors. Baltimore: Williams & Wilkins, 1984, pp 116–138.)
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Fig. 3. Distribution by age at diagnosis for patients with intracranial germinoma. (Reproduced with permission from Jennings MT, Gelman R, Hochberg F: Intracranial germ-cell tumors: natural history and pathogenesis, in Neuwell EA (ed): Diagnosis and Treatment of Pineal Region Tumors. Baltimore: Williams & Wilkins, 1984, pp 116-138.)

24 months. Among the 10 GCT cases with symptoms for 5 years or longer before diagnosis, nine had germinomas27,41,78,82,103,105,109,125 and one had germinomatous elements in a mixed endodermal sinus tumor.13 The prodrome was shorter for nongerminomatous GCT's than for germinomas (p = 0.0007). Typically, the diagnosis of an intracranial teratoma, embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma was reached within 6 months. In only 12% of cases with nongerminomatous GCT's were the patients symptomatic for more than 24 months prior to diagnosis. Prediagnosis symptomatic intervals were longer in GCT's of suprasellar origin (p = 0.001) and among females (p = 0.02).

The clinical presentation was known for 312 patients (77% of patients with germinomas and 86% of those with nongerminomatous GCT's). Patients with germinomas, which were commonly suprasellar, presented with chiasmal visual field defects (33%), diabetes insipidus (41%), and other signs of hypothalamic-pituitary dysfunction (33%). The neuroendocrine deficits included delay or regression of sexual development (16%), "hypopituitarism" (16%), and growth failure (9%). Precocious puberty was rare (5%) and occurred in three patients with tumors originating in the suprasellar region, in five with basal ganglia-thalamus tumors, and in four with pineal tumors.23,24,69,71,72,74,79,109,124,129 Human chorionic gonadotropin (HCG) or luteinizing hormone (LH) levels were known to be elevated in the serum and/or cerebrospinal fluid (CSF) of some patients with germinomas without choriocarcinomatous elements.24,64,68,69,72,91,92,134 (see also Sklar, et al.126). Less common neurological deficits at presentation were hydrocephalus (21%), obtundation (15%), Parinaud's sign (14%), pyramidal tract signs (11%), ataxia (9%), diplopia (10%), seizures (3%), choreoathetosis (2%), dementia (2%), and psychosis (1%).

Nongerminomatous GCT's presented as pineal region masses, producing hydrocephalus (47%), Parinaud's sign (34%), obtundation (26%), pyramidal tract signs (21%), and ataxia (19%). Less common symptoms were diabetes insipidus (18%) and hypothalamic-pituitary failure (19%). Choriocarcinomas were often (55%) associated with sexual precocity.65,93,148 with recognized elevations in HCG and/or LH.3,21,55,58,67,75,136

Routes of GCT Dissemination. Germ-cell tumors were disseminated both by infiltration into the adjacent hypothalamus (11%) and via the ventricular and subarachnoid pathways. Third ventricular involvement was especially common with the more malignant endodermal sinus tumor (42%) and with choriocarcinoma (42%). Spinal cord metastases were more prevalent in patients with germinomas (11%) and endodermal sinus tumor (23%). Systemic dissemination, especially to lung and bone, occurred in 3% of GCT's (choriocarcinoma,42,55,58,93,148 embryonal carcinoma,113,137 and germinoma;14,79,137 see also Rubner and Wheeler108). Abdominal and pelvic metastases developed in 10% of the 106 patients who had received ventriculosomatic shunting24,73,79,92,114,132,142,145 (see also Haimovic, et al.49).

The following correlations existed: 1) combined neoplastic involvement of the hypothalamus and third ventricle (p = 0.0005); 2) third ventricular involvement and dissemination to a noncontiguous site (p = 0.001); 3) spinal cord extension and additional metastases (p = 0.02); and 4) spinal cord metastases with pineal GCT (p = 0.003).
Correlation of Patient Characteristics with Survival

This section reports the results in the survival analysis group comprised of 263 patients who received "conventional treatment." There were 203 patients in whom surgical biopsy or resection of the primary GCT was performed, followed by radiation treatment. In 10 patients the histological diagnosis was achieved through CSF cytological examination or by biopsy of a metastasis. These patients received radiotherapy. Forty-two cases were irradiated and the histological diagnosis was made at the time of later surgery, postmortem examination, or by unspecified means. Finally, eight patients died during evaluation of the brain tumor prior to treatment. One hundred and twenty-two patients (46%) were known to have died by the time of original reporting. As mentioned, the marginal distributions of the various patient characteristics of the 263 subjects of the survival analysis group are very similar to those of the 389 patients in the natural history population. All the two-way correlations are also similar. Since medians cannot be reliably estimated when only 46% of the population has died, survival quartiles are reported in Fig. 4. (The median is the time by which half of the patients can be expected to have died; the quartile is the time by which a quarter of the patients can be expected to have died.)

Histological diagnosis exerts the greatest impact upon survival. Germinomas were associated with longer survival times than were other histological categories (p < 0.0001) (Fig. 4 left). Conversely, choriocarcinoma exhibits a singularly dismal prognosis (p = 0.009). Survival curves for patients with teratomas, embryonal carcinomas, and endodermal sinus tumors showed no significant differences, with one-half of the patients dying within the 1st year (Fig. 4 right).

The extent of disease dissemination is a predictor of survival. Neoplastic involvement of the hypothalamus (p = 0.0002), third ventricle (p = 0.02), and spinal cord (p = 0.01) has ominous associations. In the Cox models, variables that did not appear to determine survival time included site of tumor origin, sex, age, or prediagnosis symptomatic interval.

Discussion

This review of primary intracranial GCT is undertaken to define the natural history and the major biological determinants of survival in a population of 389 patients studied retrospectively. Two purposes were addressed. The first concerned criteria for the stratification of low- and high-risk intracranial GCT patients, which have not been agreed upon or widely applied. Segregation of various risk groups within a poorly understood patient population promotes more selective forms of intervention as well as comparative clinical investigation of available and experimental therapies. The second concern was that little is known regarding the etiology and developmental pathogenesis of germinal malignancies. Intracranial GCT's arise immediately adjacent to the diencephalic centers for gonadotropin regulation (see below). The germinal-embryonal character of the neoplasm and features of its natural history suggest a neuroendocrinological influence in its biological behavior. Future investigation may contribute to the generation of alternative forms of disease.
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control, including the induction of tumor differentiation or its prevention.

Segregation of Risk Groups

The emergence of extremely effective chemotherapy for testicular GCT has changed many management concepts of intracranial GCT. A brief review of the evolution of therapy is necessary to understand certain current trends. The major prognostic determinants identified in this review provide for the stratification of high-risk patients by histology and staging of the extent of disease. Diagnostic and therapeutic alternatives are discussed in light of these.

Prior to the 1970's, the attempted extirpation of a posterior third ventricular or pineal tumor carried a 25% to 70% operative mortality risk. The indications for surgical resection were restricted to apparently benign lesions or to cases of clinical deterioration despite a functioning ventriculoperitoneal shunt and prior therapeutic irradiation.118 This naturally empirically emphasized radiotherapy as the treatment of choice, which is supported by the relative success of this approach. Conventional radiotherapy has achieved 5-year survival rates of 60% to 88% (range 25% to 88%) among a group of patients with heterogeneous pineal tumors.1,61,104 Higher radiation dosages (5000 to 5500 rads) than were employed previously have reduced local recurrence rates from 47% to 10%.128 Among histologically examined germinomas, direct surgical and radiotherapeutic (5000 to 6000 rads) intervention has achieved 5- and 10-year survival rates of 75% and 69%, respectively.116

Takeuchi, et al.,134 have emphasized the radiosensitivity of pineal germinomas to dosages of 1500 rads. In Japan, where the incidence of pineal germinomas is higher than in North America, the current practice is first to irradiate a pineal tumor likely to be a germinoma with 2000 rads, and then, if the tumor regresses, to continue radiotherapy. If there is no reduction in tumor size, surgical excision is considered.46,52 Chapman and Linggood25 have shown that early radiation response is not in itself diagnostic of tumor histology or curability. The postirradiation recurrence rate of large germinomas has led Sano and Matsutani116 to advocate direct surgery and postoperative radiotherapy for all such patients except those with small or multiple germinomas. Operative safety does not appear to be the issue that it was 15 years ago. Recent advances in microsurgical technique and neuroanesthesia have allowed more than 100 patients with pineal region masses to receive surgical therapy, the only operative fatality being in a patient with metastatic disease.25,46,63,92,116,139

The most compelling reason for histological diagnosis is the identification of patients who may benefit from chemotherapy specifically directed against the GCT. Protocols using synergistically cytotoxic agents, including vinblastine, actinomycin D, bleomycin, Adriamycin, cyclophosphamide, and cis-platinum, have achieved complete remission rates of 60% to 90% against localized and metastatic testicular GCT's, in combination with surgery and irradiation.16,32,35,36,59,87 Such agents can be delivered systemically in sufficient concentration to cross the blood-brain barrier and cause significantly lengthened survival time in cases of single GCT brain metastasis.81 This experience has encouraged the use of chemotherapy with vinblastine, actinomycin D, and bleomycin among primary intracranial GCT's adjunctively or at relapse. Available anecdotal reports are reviewed in Table 3; comparison may be made with the survival curves of patients receiving conventional treatment (Fig. 4 right).

Criteria are necessary to identify those intracranial GCT patients at sufficient risk to justify toxic pharmacological intervention. There is no available large prospective study that answers this question for all histological grades of GCT of the CNS. Our retrospective review attempts to identify the major prognostic determinants among a population of conventionally treated (surgery and irradiation), histologically confirmed cases.
Two factors appear dominant in predicting outcome: histological diagnosis and the extent of disease dissemination. Germinoma is associated with significantly longer survival (p < 0.0001) (Fig. 4 left) because non-germinomatous GCT’s fail to respond adequately to conventional treatment. (Note the similarity of survival curves for each of the histological categories, regardless of intracranial (Fig. 4 right) or somatic origin.19) Furthermore, an ominous prognosis is conferred by neoplastic dissemination to the hypothalamus (p = 0.0002), third ventricle (p = 0.02), and spinal cord (p = 0.01). Caution must be exercised in the interpretation of these latter associations, as the assessment of extent of disease was made retrospectively by ante- and postmortem description.

We would first conclude that the histological diagnosis of intracranial nongerminomatous GCT represents an a priori threat of sufficient magnitude to warrant adjunctive chemotherapy in addition to surgery and aggressive radiation therapy. Furthermore, this 30-year retrospective review does not establish that surgery and radiotherapy are curative for intracranial germi- nomas, although it is the current consensus that radiation therapy is effective in disease control.116,141 The radiation therapy dosages employed are in excess of the 2500 rads proven to be effective for surgically resected Stage I testicular germinomas,3 and are more likely to produce late neurotoxicity in a pediatric population. More conservative dosage regimes (with and without chemotherapy) for this lower-risk subgroup would be safely attainable only among histologically diagnosed, surgically debulked, closely monitored germinomas.61

Considerable effort has been made to use serolog-ical biomarkers such as HCG and alpha-fetoproteins (AFP’s) as noninvasive diagnostic indicators of tumor histology. Given the present histological classification of GCT’s, there is a relative, although not absolute, correlation between CSF and serum biomarkers and the tumor’s histological category. Elevated HCG and/or AFP levels in serum or CSF have been said to be suggestive of a nongerminomatous GCT. Among primary intracranial GCT, HCG elevations have been reported in patients with choriocarcinomas,3,8,21,39,42,48,55,67,75,136 (see also Sklar, et al.,126), embryonal carcinomas,3,48,64,94 teratomas,24,52,63 and endodermal sinus tumors.3 Supra-physiological levels of LH have been noted in cases of germinoma,49,72,75,122,134 embryonal carcinoma,64 and choriocarcinoma.58,67 The LH elevations may be due to cross-reactivity with beta-HCG in the radioimmunoas- say, a not uncommon finding with testicular GCT.34 Alpha-fetoprotein levels have been elevated in patients with intracranial germinoma,3 teratoma,24,52,63,136 embryonal carcinoma,3,8,24,48,94,135 endodermal sinus tumor3,6,123,135,142,147 and choriocarcinoma.8,48

It is controversial whether HCG production by a germinoma alters the patient’s prognosis.17,88 The presence of these biomarkers has been shown to be a grave prognostic sign in patients with testicular GCT15,40,130 and may be for those with intracranial germinal malignancies as well.8 This reflects the generally poorer prognosis of tumors with nongerminomatous elements and may possibly be a specific effect of gonadotropin secretion (see below).

Our second conclusion is that a full extent of disease staging at initial presentation is crucial to the identification of high-risk patients. Germ-cell tumor dissemination to the hypothalamus, third ventricle, and/or spinal cord warrants neuraxis irradiation and systemic chemotherapy. The most sensitive indicator of hypothalamic infiltration is the neuroendocrinological evaluation of the hypothalamic-pituitary axis.47 Roentgenological investigation includes computerized tomog-raphy (CT) scanning (the differential CT appearance of pineal tumors is reviewed elsewhere63), gas or iodopam- idol cisternography, if necessary, and myelography. Se-rial CSF cytological examinations may allow preemptive treatment of spinal cord metastases prior to their appearance on myelography. Although CSF cytology has been abnormal in 60% of pineal germinomas52,115 a negative cytology does not exclude subarachnoid seed- ing.25,63,128 The identification and localization of HCG, LH, and AFP secretion may be made through comparison of CSF and serum levels. Cerebrospinal fluid HCG levels are considered positive if they are greater than 2% of the serum levels.119 The CSF concentration of AFP may not be a reliable marker of CNS involvement.81,119

Both the extent of dissemination and response to therapy may be monitored using these markers in positive cases. Current practice for the management of testicular GCT advocates monthly reevaluation for the 1st year, and bimonthly for the 2nd year.89 Relevant features of this evaluation would consist of physical examination, serum (and CSF) biomarker study, chest radiography, and CSF cytology. Obtaining CT scans may be advisable every 3 months as well as before and after chemotherapeutic courses. Increasing attention is being paid to lactic dehydrogenase-I isoenzyme in the monitoring of testicular GCT. This marker correlates with tumor bulk, and is considered as significant a prognostic indicator as an elevated HCG or AFP.15 Bone marrow examination may be indicated for tumors such as embryonal carcinoma and choriocarcinoma, which demonstrate an increased risk for systemic spread.

The issue of “prophylactic” irradiation of the neuraxis for cases of pineal tumors is confounded by the paucity of information on prospective multimodality examination and long-term follow-up review, and the infrequent correlation with histological diagnosis.61 Large series of suprasellar and pineal germinomas indicate a 10% to 20% (range 5% to 57%) incidence of spinal metastasis.25,52,61,116 Three studies61,128,141 have found a higher incidence of spinal dissemination among patients undergoing biopsy for diagnosis of germinoma in comparison to unbiopsied patients. This finding has not been substantiated in the experience of oth-
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Pathogenesis of Intracranial Germ-Cell Tumors

A developmental etiology for intracranial GCT's is favored by certain features of their natural history: the embryonal character of the neoplasm, the specificity of the site of origin, the sharply defined age range, the skewed sex distribution, and the protracted prodrome of many germinomas. While these suggest the antecedent presence of germ cells, it is uncertain whether this is due to germinal malmigration, embryonic "cell rests," or a localized hamartomatous or dysplastic process. To understand why the suprasellar and pineal regions may serve as sanctuaries for undifferentiated germinal cells, it is necessary to demonstrate the existence of an ontogenic, synaptic, and functional interrelationship between the hypothalamus adjacent to the suprasellar cistern and the pineal gland.

During neuroembryogenesis, both the ventral hypothalamus and epiphysis are identifiable by 35 to 38 days (Streeter's Stage XV). The early maturation of these diencephalic structures coincides with the major migration phase of human germ cells from the hindgut and allantois (posterior yolk sac) to the germinal ridges. Normally, in fetuses older than 60 days (Streeter's Stage XXIII, 35 mm), extragonadal germ cells disappear. Germ cell malmigration may explain the occurrence of GCT's in the sacroccygeum, retroperitoneum, and mediastinum. The presence of GCT in specific diencephalic loci suggests that local factors play a major role in either drawing germ cells to these sites or altering their normal patterns of development.

Within the mature diencephalon, the ventral hypothalamus and the pineal gland are directly entrained in the regulation of a major neurophysiological function, namely, the circadian rhythm. There exists a synaptic connection between the hypothalamic suprachiasmatic nucleus, which lies adjacent to the suprasellar cistern, and the pineal gland. This is created by the accessory optic tract, linking the optic chiasm to the suprachiasmatic nucleus, and a direct connection traversing the lateral hypothalamus to the intermediolateral cell column of the upper thoracic spinal cord. These neurons provide sympathetic innervation to the pineal gland through the superior cervical ganglion. A functional purpose of this entrainment may be the regulation of gonadotropin activity. Within the suprachiasmatic and preoptic nuclei lie the follicle-stimulating hormone- and LH-releasing hormone secretory neurons of the hypothalamus. Antagonism within this system is provided by the pineal gland through an antigonadotropic substance other than melatonin or vasotocin arginine. An additional role for the pineal gland in the neuroendocrinological regulation of neoplastic growth has also been suggested.

Germ-cell tumors of the CNS arise within or adjacent to the diencephalic centers for the regulation of gonadotrophic activity. Gonadotropins are implicated in the pathogenesis of CNS germinal tumors not only in the determination of their site of origin but also as carcinogenic inducers. Our review suggests that the neuroendocrinological events of puberty are an "activating" influence in the expression of malignant behavior among intracranial GCT's. Supporting evidence for an inductive or transforming role of gonadotropins (steroidal sex hormones or the gonadotropin-releasing hormones) on germinal tumors include the following findings. 1) Germ-cell tumors have been associated with increased gonadotropin secretion in cases of cryptorchidism, testicular feminization, and gonadal dysgenesis. 2) The observation has been made that gonadotropin-secreting GCT's are associated with a worsened prognosis, even for tumors within the same histological category. This may be the result of LH-releasing hormone induction of more malignant HCG-secreting syncytiotrophoblastic elements within the GCT. 3) The incidence of GCT is relatively increased during infancy and adolescence, periods of changing gonadotropin exposure. 4) Elevated gonadotropin levels may persist after unilateral orchidectomy in cases of testicular GCT. These elevations have been shown to be unrelated to GCT metastases and may not be detected in extracts of the primary tumor or the metastases. 5) In tissue culture, androsterone accelerates the growth of certain testicular tumors.

The presence and functional role of sex steroid, gonadotropin, and gonadotropin-releasing hormone membrane receptors are yet to be shown for intracranial GCT. Should gonadotropins be demonstrated to direct differentiation among GCT's toward nongerminomatous elements (with consequent worsening of prognosis), pharmacological prevention of this may provide an additional method of disease control.

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