Clinical case

The role of chemotherapy in intracranial germinoma: A case report

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Summary

Background: The case of a 29-year-old man with histologically proven simultaneous germinoma (seminoma) of the pineal gland and a stage I embryonal carcinoma of the testis is reported. An intradural metastatic lesion from the pineal germinoma was diagnosed at the level of the first thoracic vertebra. Treatment, after inguinal orchiectomy, was chemotherapy only, rather than conventional radiotherapy for the pineal germinoma.

Methods: Therapy consisted of bleomycin (B), etoposide (E) and cisplatin (P). MRI was used to assess the effectiveness of BEP chemotherapy.

Results: A complete remission of the pineal gland germinoma and the epidural metastasis was documented after two cycles of BEP chemotherapy and after 15 months of follow-up the patient remains free of relapse.

Discussion: The pathogenesis of simultaneously occurring germinoma of the pineal gland and embryonal cell carcinoma of the testis is discussed. The choice of therapy in these circumstances is a matter of debate and the good result of chemotherapy alone in this patient suggest that primary chemotherapy may be the therapy of choice in patients with pineal germinomas.

Key words: BEP chemotherapy, embryonal carcinoma testis, germinoma, pineal gland

Introduction

Germ cell tumors (GCT) are primarily gonadal neoplasms, but may also arise extragonadally in the midline structures of the body, especially in the sacro-coccygeal, retroperitoneal and mediastinal region. Intracranially they also tend to arise in the midline in the pineal and hypothalamic/intrasellar regions. There is little or no information available about synchronous or metachronous extra central nervous system (CNS) located GCT. Primary CNS germinomas are highly radiosensitive and curable in most patients (60%-80%) with a course of therapeutic radiotherapy [1]. Radiotherapy options include craniospinal therapy with a boost to the primary site for localized and/or disseminated disease [2] or involved field therapy alone for localized disease [3]. Several clinical trials have confirmed that CNS germinomas are also highly responsive to chemotherapeutic drugs, not only on recurrence after radiotherapy but also in newly diagnosed patients [4-6, 12, 15-20]. Cisplatin-based chemotherapy followed by low dose radiotherapy (24-30 Gy) may have the same therapeutic results as high dose radiotherapy only (50-55 Gy) but without delayed damage to the CNS primarily manifested as growth retardation, neuroendocrine, and cognitive deficiencies [7]. Chemotherapy studies may eventually permit elimination of radiotherapy for patients with CNS germinomas. We report the result of chemotherapy alone in a patient with concommitant gonadal and CNS germin cell neoplasia.

Case report

A 29-year-old man presented with a history of three months of headache, vomiting, blurred vision and diplopia. Magnetic Resonance Imaging (MRI) demonstrated a round lobulated tumor with a diameter of 3 cm between the mesencephalon and corpus callosum obstructing the aquaduct causing hydrocephalus (Figure 1a). An endoscopic ventriculo-cisternostomy was performed of the floor of the third ventricle by a flexible-controlable endoscopy. During the operation biopsies were taken from the posterior part of the wall of the third ventricle through a burr hole to the basal cistern.

Histology of the pineal gland tumor revealed tumor cells arranged in a diffuse, sheet-like pattern interrupted by small branching fibrous septa containing an inflammatory infiltrate consisting of lymphocytes. The cells were lightly eosinophilic with uniform, centrally placed nuclei containing one or two prominent nucleoli. Glycogen was present in the cytoplasm. Mitotic figures were easily found. Immunohistochemical investigation showed positivity for placental alkaline phosphatase (PLAP) and focally for β-HCG. The tumor cells were negative for cytokeratin (CK 10, 17, 18 and MNF 116), AFP and Ki-1 (CD30). The histologic conclusion was that this was a seminoma (germinoma) of the pineal gland (Figures 2 and 3).

Cytological examination of the ventricular cerebrospinal fluid (CSF) revealed malignant cells compatible with the histology of the primary tumor. Staging com-
Figure 1. (a) Magnetic resonance imaging (MRI) demonstrating a tumor, diameter 3 cm, between mesencephalon and corpus callosum. (b) MRI demonstrating leptomeningeal metastasis at level of the first thoracic vertebra.

Figure 2. Histology (H & E, 100x) of the pineal gland tumor. Cells are arranged in a diffuse sheet-like pattern interrupted by fibrous septa containing infiltrates of lymphocytes. The cells are lightly eosinophilic, have uniform nuclei containing 1-2 prominent nucleoli. Abbreviation: H & E - Haematoxilin and eosin.

Figure 3. IHC staining of the pineal gland tumor. Cells are negative for cytokeratin (MNF 116, 50x). Abbreviation: IHC - immune histochemical.

Computer tomography of the abdomen and chest did not reveal intra-abdominal or intra-thoracic metastases. MRI of the thoracic and cervical spine showed an intradural extramedullary metastasis at the level of the first thoracic vertebra (Figure 1b).

Ultrasonography of the testicles showed a lesion with a diameter of 9 x 12 mm in the right testicle. Inguinal orchiectomy was performed and histological investigations revealed a tumor with cohesive groups of primitive, anaplastic epithelial cells arranged in diffuse sheets with prominent foci of eosinophilic coagulative necrosis. The tumor cells had variably staining, abundant cytoplasm and large, vesicular, irregular nuclei with prominent nucleoli. The mitotic rate was high. Immunohistochemistry of the tumor cells showed strong cytokeratin positivity (C10, 17, 18 and MNF 116) and focal PLAP positivity and Ki-1 (CD30) positivity. AFP and β-HCG staining were negative.

The histologic diagnosis was that this was an embryonal carcinoma of the testis (Figures 4 and 5).
### Table 1. Treatment and outcome of patients with intracranial germinomas and non-germinomas.

<table>
<thead>
<tr>
<th>Investigator, reference</th>
<th>Germinoma (no. of pts)</th>
<th>Non-germinoma (no. of pts)</th>
<th>Radiotherapy (Gy)</th>
<th>Chemo/radiotherapy</th>
<th>Chemotherapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao [16]</td>
<td>7</td>
<td>9</td>
<td>30-50</td>
<td></td>
<td></td>
<td>3 of 7 recurr. germ.</td>
</tr>
<tr>
<td>Sawamura [17]</td>
<td>29</td>
<td></td>
<td>45-50 (n = 10)</td>
<td>PEA/cyclophos/MTX + 24 Gy</td>
<td></td>
<td>6 of 9 recurr. non-germ</td>
</tr>
<tr>
<td>Balmaceda [18]</td>
<td>45</td>
<td>26</td>
<td>50 (n = 31)</td>
<td>PVB/PE (n = 19) + 30 Gy</td>
<td>CE/BLM 35/71</td>
<td>1 of 29 recurr.</td>
</tr>
<tr>
<td>Matsutani [19]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PVB/CE (n = 3) 35%−70% 10 years surv (non-germ.)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Gy – gray, P – cisplatin; E – etoposide; A – doxorubicin; MTX – methotrexate; Iphos – ifosphamide; C – carboplatin; B/BLM – bleomycin; V – vinblastin.

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**Figure 4.** Histology (H & E, 100x) of the testicular tumor, with groups of primitive, anaplastic epithelial cells arranged in diffuse sheets. Cells have variable staining, abundant cytoplasm and large, vesicular, irregular nuclei with prominent nucleoli.

**Figure 5.** IHC staining of the testicular tumor show strong cytokeratin positivity (MNF 116, 25x).

At the end of the diagnostic work-up we concluded that this 29-year-old man had a germinoma of the pineal gland and a leptomeningeal metastasis, with synchronously a non-metastasized embryonal carcinoma of the right testicle. He was treated with four courses of bleomycin 30 mg i.v. dd on days 2, 8 and 15, etoposide 100 mg/m² i.v. dd on days 1 through 5 and cisplatin 20 mg/m² i.v. dd on days 1 through 5 (BEP). After two courses of BEP chemotherapy no tumor remained on MRI of the brain or cervico-thoracic part of the spinal cord. Fifteen months after discontinuation of BEP chemotherapy no signs of relapse have been seen on MRI of the CNS.

**Discussion**

Extragonadal GCT may arise in midline structures of the body, including the pineal gland, mediastinum and retroperitoneum. The simultaneous presentation of germinoma of the pineal gland and testicular embryonal carcinoma has not been described. The presentation of the tumor in this case supports Cohnheim and Sano’s theory [8, 9] about development of GCT outside the gonads. It is most widely accepted that at the beginning of the third week of embryogenesis the primitive streak originates at the caudal part of the embryonic disc. This is formed by movement of proliferating disc cells towards the midline to enter the primitive groove. These cells leave the basal layer of the primitive groove and migrate laterally with the moving cells of the mesoderm to the area of the future cranium [9]. When the neural plate is formed these migrated cells may be enfolded into the neuraxis and may later develop the intra-cranial GCT.

The different histological features in the testicular tumor and the pineal gland in our patient suggests that both neoplasms arose from the same primordial germ cells of the embryonic disc before migration of these cells, but that both mutated cells develop differently in different environmental circumstances causing a germinoma in the pineal gland and embryonal cell carcinoma in the testis.

The majority of germinomas arise in the suprasellar region and present commonly with visual impairment,
symptoms related to obstructive hydrocephalus and hypothalamic-pituitary failure. They are exclusively radio-sensitive [1–3, 10, 11, 19] with five-year survival rates of 65%–95% being reported. However, the optimal size of the radiation field has not yet been defined, because of subclinical intraventricular and/or spinal CSF metastases which occur in up to 60% of all cases [12]. In addition, delayed side effects of radiotherapy such as brain atrophy, vasculopathy and secondary malignancies may cause severe problems, particularly in children and young adults [13, 14]. In order to avoid deleterious effects of irradiation, systemic chemotherapy either alone or in combination with irradiation has been tried [1, 2, 4–6, 12, 15–20].

The choice of chemotherapy instead of radiotherapy was in our case based on the excellent response of systemic GCT to similar regimens and the results of the studies that have used chemotherapy for GCT of the CNS (5–7, 12, 17–20]. These studies showed: a) the curative potential of cisplatin in combination with etoposide in extracranial germ cell tumors, b) the effectiveness of chemotherapy against CSF dissemination, c) that it might be possible to omit the radiotherapy and the toxic effects of radiotherapy. In this case there was the added advantage that BEP would be useful adjuvant treatment for the simultaneously occurring GCT in the testis. A particular reason not to use radiation therapy was the possibility of long-term sequelae of radiation therapy, including intellectual deterioration, growth retardation, endocrine dysfunction and hearing loss in this young man. The good response to therapy in this patient suggests that four courses of BEP chemotherapy may be effective in CNS germinoma (pineal gland and leptomeningeal localisations) but longer follow-up and more patients treated with chemotherapy alone are needed.

References

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