ERATOMAS comprise a group of germ cell neoplasms composed of tissues with cellular phenotypic traits associated with the three classic germ layers and are considered to be the neoplastic counterparts of embryonal tissue. They account for 3% of all childhood tumors, with the majority occurring in the sacrococcygeal regions and in the gonads. The histological appearance of these tumors is strikingly similar, regardless of the anatomical site of origin. Intracranial teratomas are rare, constituting approximately 0.5% of all intracranial neoplasms. However, in series consisting of young patients exclusively, the incidence is substantially higher.

Teratomas are classified into three groups: mature teratomas, immature teratomas, and teratomas with malignant elements. The hallmark of immature teratomas is the conspicuous presence of cellular populations that retain an embryonal character and display phenotypic differentiation attributed to the three germ layers. The clinical management of these lesions is unclear, due in part to their low incidence and to an incomplete understanding of their natural history. Although the potential for phenotypic differentiation and cellular maturation within immature teratomas arising in the gonads is well documented, this has not been described in the intracranial tumors. In the present report, the authors describe two cases of intracranial immature teratomas, one involving the pineal region and the other involving the left frontotemporal lobes, which underwent cellular differentiation and maturation. At initial resection, the tumors from both cases were composed predominantly of primitive neuroepithelial tissue that was admixed with immature and differentiating mesenchymal and epithelial structures. No foci of germinoma, endodermal sinus, choriocarcinoma, or embryonal carcinoma tissue were present. Subsequent resections in both cases revealed an absence of immature tissue. The tumor in Case 1 contained only differentiated epithelial and mesenchymal tissue with no neuroepithelial component, whereas the tumor in Case 2 demonstrated abundant mature neuronal and glial tissue. These two cases from different intracranial sites suggest that spontaneous maturation may be a significant aspect of the natural history of intracranial immature teratomas.

KEY WORDS • teratoma • prognosis • intracranial neoplasm • chemotherapy

The potential for phenotypic differentiation and cellular maturation within immature teratomas of the ovary and testis is well known; however, this process has not been documented in the intracranial tumors. In the present report, we describe two cases of intracranial immature teratoma with a benign clinical course that was accompanied by loss of immature elements.

Case Reports

Case 1

History. This 9-year-old boy presented to another institution with headache, blurred vision, and ataxia. Computerized tomography scanning showed a large cystic tumor in the pineal region. A putative metastatic lesion at the level of C-2 was visualized by magnetic resonance imaging. Serum α-fetoprotein (AFP) was mildly elevated at 49 ng/ml. Serum human chorionic gonadotropin (HCG) and cerebrospinal fluid levels of AFP and HCG were normal. The patient underwent posterior fossa exploration and a subtotal resection. After the first surgery, he received four courses of combined chemotherapy (cyclophosphamide, bleomycin, and etoposide) and craniospinal axis radiation.
Maturation of immature teratomas

irradiation. One year after treatment, follow-up MR imaging revealed enlargement of the residual pineal mass (Fig. 1 left); however, at this time there was no clinical or radiological evidence of metastatic disease, and no C-2 lesion was detected. Serum AFP was within normal limits. The patient was referred to our institution and underwent a posterior transcallosal, near-total resection of the tumor. The patient is alive and well 54 months after his second operation and exhibits substantial improvement in his neurological deficits (Fig. 1 right).

Histopathological Findings. Examination of multiple fields from the initial specimen demonstrated an immature teratoma, with epithelial and mesenchymal components, that was predominantly constituted by primitive neuroepithelial cell populations. The primitive neuroepithelial component consisted of a pseudostratified columnar epithelium often arranged in tubules or extensive rosettes, recalling the neuroepithelium of the embryonal ventricular germinal matrix. Mitotic figures were conspicuous in both the primitive neuroepithelium and in the surrounding cell populations composed of primitive neural cells. Differentiating glia and neuroblasts were admixed in these adjacent fields. The primitive neuroepithelium of pseudostratified tubular formations and differentiating neuroblasts demonstrated strong immunoreactivity for the neuron-associated class III β-tubulin isotype (Fig. 2), which is often expressed during early stages of neuroblastic differentiation. Extensive study of multiple sections did not detect any evidence of a malignant cellular component consisting of embryonal carcinoma, choriocarcinoma, and/or yolk sac endoderm.

Extensive study of multiple blocks of the recurrent tumor did not reveal any primitive cell populations, including the previously conspicuous neuroepithelial component. Only differentiated epithelial and mesenchymal tissues were found after extensive analysis (Fig. 3).

Case 2

History. This newborn presented at birth with severe
proptosis. Computerized tomography scanning and MR imaging demonstrated an intracranial mass involving the left anterior and middle cranial fossa that extended into the left orbit (Fig. 4 left). He underwent a left frontotemporal craniotomy and subtotal resection of the tumor. At the time of initial surgery, serum HCG was normal but his serum AFP level was 9930 ng/ml. His serum AFP level was reduced to 1167 ng/ml within 4 weeks of the first surgery. Over the next 6 months, the residual tumor increased in size, and the child underwent two extensive, but subtotal, resections. After the third surgery, at age 7 months, there was no neuroimaging evidence of tumor recurrence. The child is now 6 years old and developing well with no evidence of recurrent tumor (Fig. 4 right).

**Histopathological Findings.** The histopathological findings in the specimen from the initial resection were consistent with an immature teratoma and included glandular epithelium (Fig. 5 right) and immature/differentiating mesenchymal tissue in addition to a predominance of primitive neuroepithelial tissue (Fig. 5 right). Ependymoblastomatous and transitional rosettes were admixed with groups of differentiated glia and immature neuroblasts (Fig. 5 right). These areas of neuroblastic differentiation were immunoreactive for the class III β-tubulin isotype.

The recurrent tumor specimen demonstrated abundant mature neuronal and glial elements as well as differentiated epithelial structures and mesenchymal tissues (Fig. 6).

**Discussion**

Intracranial teratomas account for 2% of intracranial tumors in children younger than 15 years of age. The tumors preferentially arise in the midline and occur more commonly in male than female patients. The usual location is in the pineal region, followed by the region of the third ventricle and the fourth ventricle, respectively. In the absence of a clear classification of intracranial teratomas, these neoplasms have been described in different terms such as solid teratomas, malignant teratomas, embryonal teratomas, teratocarcinoma, dysembryoma, and teratoblastoma. The World Health Organization classification of intracranial teratoma considers three histological variants: mature, immature, and malignant. This scheme is clear, easy to apply, and should be used to classify teratomas uniformly. Additional confusion has been added because mixed elements can be found in the same tumor; thus, intracranial teratomas often have been considered inappropriately in the same category as mixed germ cell tumors. Therefore, it is crucial that extensive sectioning of the surgical specimen is performed to make the correct diagnosis and exclude mixed and/or malignant elements.

Histopathological differentiation of immature teratomas to mature forms has been reported in ovarian teratomas following chemotherapy, or spontaneously, and in testicular germ cell tumors after chemotherapy and radiotherapy. DiSaia and coworkers first reported three cases of maturation of immature ovarian teratoma following chemotherapy. The patients responded well and sustained remission for several years. In our two cases, histological maturation was identified after only 1 year in the first patient and after only 6 months in the second; the first patient had also received chemotherapy and radiation therapy.

The maturation of human immature teratoma is probably a consequence of its origin from multipotent embryonal cells, with the potential and tendency to convert from an immature to a mature state just as normal embryos. Kleinsmith and Pierce studied differentiation of experimental tumors by injecting single cells of mouse malignant teratoma into the peritoneal cavity of other mice. They found that the successfully implanted tumors had both embryonal cancer cells and many well-differentiated cells of various kinds. This confirmed the possibility of maturation of malignant teratomas in experimental ani-
mals and the embryonal cell to be a multipotent cell capable of producing various well-differentiated daughter cells.

Differentiation of immature teratomas, previously considered a rare event, may actually occur more frequently than originally thought. Moskovic and coworkers have recently reported a series of seven patients with metastatic immature teratoma of the ovary followed between 1983 and 1989. All seven patients underwent reoperation for recurrent disease and showed tumor maturation on second-look laparotomy. The maturation process can take quite a long time, and a tendency in immature teratomas of childhood toward gradual maturation with increasing age has been reported. Liu. et al., reported 10 patients, originally diagnosed with immature teratomas and recurrence, who underwent a total of 14 reoperations. All of the recurrent tumors consisted of various tissues derived from three germ layers. Pathological grade of the recurrent tumor was closely related to the length of the interval between the first operation and the time of recurrence. In seven cases with a time interval of less than 1 year, the recurrent tumors were all of the immature type. In another seven cases in which the time intervals were over 12 months, however, the recurrent tumors were mostly the mature type. Most of the cases that received chemotherapy previously had recurrent tumors of the mature type, whereas the majority of the cases that did not receive chemotherapy had recurrences consistent with immature tumors. However, in their series, three cases not receiving chemotherapy also transformed into more mature tumors.

Because of their rarity, the natural history of intracranial immature teratomas is largely unknown. The prognosis has usually been considered grim because of their progression and their difficult surgical location. In 16 cases of immature teratomas reviewed by Bjornsson, et al., seven patients had died, and, of these, three showed evidence of extraneural spread and another three showed evidence of neural dissemination. In their series, the 5-year survival rate was less than 40%.

However, the management of these lesions may have changed considerably in the past 10 years, largely due to the willingness of neurosurgeons to resect previously considered “inaccessible tumors.” The development of effective chemotherapeutic protocols for systemic teratomas may also have an ultimate impact on the prognosis of patients with their central nervous system counterparts. However, as illustrated in our two cases, the role of chemotherapy in intracranial immature teratomas is still not explicitly clear. Both tumors matured quite rapidly, although it could be speculated that the lack of a neuroepithelial component in the reoperative specimen of Case 1 might be attributable to adjunctive therapies.

From a review of the literature concerning the behavior of immature teratomas at extracranial sites and from our anecdotal case reports, an aggressive surgical approach to the management of these tumors appears warranted. In...
some cases, surgical debulking, with or without chemotheraphy, can provide necessary, temporary relief of mass effect while the tumor biology changes. It is conceivable that immature and mature teratomas represent a temporal continuum, as opposed to isolated diagnoses. Therefore, a more aggressive management that includes surgery, judicious use of chemotherapy, and, if necessary, reoperation on recurrences is suggested in the hope that some of these tumors may shift to a mature form with time.

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