Endoscopic Histologic Mapping of a Mixed Germ Pineal Tumor
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Key words
- Biopsy
- Diagnemimoma
- Endoscopy
- Pineal tumor
- Ventriculostomy
- Yolk sac

INTRODUCTION
Pineal region tumors account for 3.5%−5% of intracranial tumors in children, 50%−70% of which are germ cell tumors (GCTs).4 Their accurate diagnosis is important for determining the treatment strategy and prognosis5−8 especially in the mixed GCT subgroup, in which the identification of all the tumor histologic components represents a real challenge for the neuropathologist.4

Despite the technical advances in neuroimaging techniques, radiologic findings are not specific enough for differential diagnosis.1,4 Current neuroendoscopic approaches allow for a tumoral biopsy to be performed, although several technical questions remain about the procedure and different negative biopsy rates have been described,10−12 most being those with a low number of samples and limited to a small tumoral area.

We describe a pineal mixed GCT histologic mapping procedure through an endoscopic supraorbital approach and outline the technical pitfalls that need to be overcome to obtain an accurate diagnosis.

CASE DESCRIPTION:
A 13-year-old male with no previous medical history was admitted to the emergency department with headache and seizures. In the previous month, he had had 3 generalized, self-limited, tonic episodes with consciousness impairment, the last one just before admission. On admission, he had mild consciousness impairment without any motor or sensory focal signs. Computed tomography (Figure 1A) showed a large pineal tumor with secondary supratentorial hydrocephalus. Based on his clinical and radiologic features, the patient underwent an urgent endoscopic ventriculostomy and biopsy.

Operation
An endoscopic echo-guided dual approach was chosen using a 2 burr-hole strategy with 2 different rigid endoscopes. Burr holes were enlarged to obtain minicraniotomies on both sides. Ventriculostomy was performed with a standard procedure through a right prefrontal frontal minicraniotomy to access the tuber cinereum in the floor of the third ventricle with a 6-mm-diameter endoscope and a 0° lens (Minop [Aesculap, Center Valley, Pennsylvania, USA]). At this stage, cerebrospinal fluid (CSF) samples for microbiology, biochemistry, and tumoral markers were collected. A second, more anterior, ipsilateral supratentorial minicraniotomy was used to reach the pineal tumor through the Monro foramina in the posterior part of the third ventricle with an 8-mm-diameter endoscope with a 30° lens (Minop InVent [Aesculap]).

Once the tumor was reached, several samples were taken using a multiprobe approach (Figure 2) to map the tumor histologically and therefore enhance the pathologic diagnosis.

Fifteen small tumor fragments were extracted, proceeding in a clockwise direction. The postoperative computed tomography scan did not show intraparenchymal
bleeding or any further complications other than a minor fronto-orbital epidural hematoma without any clinical impact. This hematoma was treated conservatively, with a favorable clinical evolution.

**Laboratory and Pathologic Findings**

α-Fetoprotein (AFP) and β-human chorionic gonadotropin in serum and CSF were assessed. Serum AFP level was slightly increased (89.8 ng/mL; reference values, 0–10 ng/mL) and serum β-human chorionic gonadotropin level was normal. CSF AFP and β-human chorionic levels were also increased (4.9 ng/mL and 0.414 ng/mL, respectively).

Histologic examination showed a giant germ cell neoplasm (Figure 3) with 3 different intermixed patterns. One fragment was diffusely infiltrated by a uniform proliferation of large germ cells with vacuolated cytoplasm and prominent nucleoli. The strong positivity for placental alkaline phosphatase and D2-40 confirmed the diagnosis of a germinoma component. In other fragments, foci of yolk-sac tumor with a primitive tubular pattern were intermixed with a heterogeneous combination of immature mesenchymal matrix with chondroid differentiation and different glandular components. The immunohistochemistry study showed a focal positivity for AFP and cytokeratins. The diagnosis of a pineal mixed germ tumor with germinoma, yolk sac, and possible immature teratoma component grade IV (World Health Organization, 2016) was made based on these findings.

**Postoperative Course**

To complete the case assessment, cerebral and spinal magnetic resonance imaging (MRI) were performed (Figure 1B–D). It showed a well-delimited lobulated pineal tumor (62 × 21 × 25 mm; 20 mL), with a homogeneous low signal in T1-weighted images and isointense in T2-weighted and fluid-attenuated inversion recovery images, as well as small cystic areas and eccentric calcifications. The tumor showed a homogeneous enhancement after intravenous contrast administration. In addition, the third ventriculostomy permeability and a mild reduction in the hydrocephalus were confirmed.

The patient was treated with chemotherapy (cisplatin, ifosfamide, and etoposide) and radiation therapy with an excellent response (Figure 1E–F). A posterior infratentorial supracerebellar approach was performed to resect the residual lesion, without complications (Figure 1G–H). The histologic examination of this residual lesion showed a complete mature teratoma.

**DISCUSSION**

Variety in histopathologic diagnosis of pineal region lesions stems from the wide
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In the pediatric population, GCTs have more than 25% of cases, known as mixed GCT. In most cases, mixed GCT consists of a combination of a germinoma component and a nongerminomatous GCT (NGGCT) component.2,3

According to its prognosis, a mixed GCT could be included in the intermediate or poor prognostic groups. Patients with an NGGCT other than teratoma are classified in the poor prognostic group, with a 5-year survival rate of less than 50% if they have a malignant NGCGT component and their prognosis is determined by the NGGCT component.4

The accuracy of the initial histologic diagnosis is relevant in choosing treatment and establishing prognosis.2,5 The yolk-sac component finding in the case presented here has a crucial role in selecting the therapeutic approach and, more importantly, modified the prognosis significantly. If this component had not been identified, and considering the serum markers, the patient would have been treated as having a mixed GCT with an immature teratoma component, altering his prognosis and his projected chances of survival dramatically.

Taking into account the importance of the histologic diagnosis, the current approach for pineal region tumors, which often present with hydrocephalus, includes ventriculostomy and tumor biopsy. Despite the predilection for carrying out both procedures simultaneously, performing an endoscopic biopsy in that case, several technical questions remain.6

Neuroendoscopic biopsy has been described as a safe procedure, with a complication rate lower than 13% and without significant long-term morbidity. Moreover, it has the advantage that a concomitant third ventriculostomy can be performed. However, sampling errors may occur, particularly in low-grade glial tumors.7

In contrast, stereotactic biopsy appears to be slightly safer and more accurate than the single burr-hole endoscopic approach, remaining the best option for the diagnosis of pineal region tumors without hydrocephalus, according to some investigators.4,6,7,8 This subject has recently been addressed by Balossier et al.,4 in a case series study in which they compare both approaches using a large series of pineal tumor biopsies. These investigators found that in the stereotactic biopsy series, the accuracy rate was higher and the perioperative morbidity was less than in the single burr-hole strategy endoscopic approach group.

Nevertheless, the differences in perioperative morbidity could be explained by the displacement of the fornix and other structures that surround the foramina of Monro in the single burr-hole strategy used in the endoscopic group, and comparisons with the dual burr-hole approach have not been made. Moreover, these differences are based on the diagnostic procedure only, because the stereotactic approach does not allow simultaneous treatment of the hydrocephalus and an additional procedure is required.

On the other hand, the differences between the MRI spectroscopy patterns of the different components of a mixed GCT could guide the stereotactic sampling. This principle could be apply in a navigated dual burr-hole approach allowing MRI spectroscopy-guided biopsy under direct visualization of the tumor.5

Furthermore, when an endoscopic biopsy is the chosen approach, the question remains as to whether to perform a single burr-hole or a dual burr-hole strategy. Nevertheless, there is no evidence indicating which approach is more efficient in obtaining histologic samples.
suitable for diagnosis. The recommendations to use one or the other are based on tumoral and anatomic features, but the surgeon’s preferences, experience, ability, and technical support are also important factors.

In the single burr-hole approach, the entry point is placed 2–3 cm anteriorly to the Kocher point, allowing both procedures to be performed at once with a rigid endoscope. In a large series, the diagnostic rate was only 85% using this procedure. Moreover, this technique can be assisted with a neuronavigation system, achieving good results, as shown in Knaus et al.’s series, and it can also be performed with the aid of flexible endoscopes, with some disadvantages, such as the smaller working channel and the worse image definition.

Regarding the 2 burr-hole technique, Chibbaro et al. described a 20-case series of pineal lesions approached with a dual burr-hole strategy, with a 100% rate of

Figure 3. Histologic examination. (A, B) Two endoscopic biopsy fragments with different germ cell tumor histologic patterns (hematoxylin-eosin (HE), original magnification x2). The regions in the boxes (*, **, and *** ) are enlarged in the figures C, D, and E, respectively. (C, F) The germinoma component is composed of uniform large cells with clear cytoplasm (HE, original magnification x40) and strong positivity for placental alkaline phosphatase (immunohistochemistry [IHC], original magnification x20). (D) Yolk-sac tumor pattern intermixed with intestinal glandular epithelium (HE, x20). (E) Primitive mesenchymal tissue from immature teratoma component (HE, original magnification x20). (G) AFP focal positivity in yolk-sac tumor areas (IHC, original magnification x10). (H) Cytokeratin-positive immunolabelling (IHC, original magnification x20).
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Sucessful biopsies. The accurate diagnosis in the case presented could be related to the 2 burr-hole rigid endoscope approach used (Figure 1C–D). The resulting working angle and a large working channel endoscope that allows more efficient instrument movements enable the surgeon to perform histologic mapping of the tumor with accurate control of the sample sites (Figure 2C). Among other advantages, it reduces the risk of fornice damage with less tissue displacement. In addition, it allows a frontal visualization of the tumor, whereas the angle with a single burr-hole necessitates samples to be taken from its inferior part. Endoscope-assisted navigation over MRI spectroscopy is possible.

Considering that the particular heterogeneity of mixed GCT makes it difficult to obtain an accurate diagnosis in small specimens, the number of tissue samples taken and the strategy for obtaining them are significant technical factors. It is not clear if taking more samples results in a more accurate diagnosis without increasing complications. Besides, the number of samples is not standardized, as can be seen from several case series, in which the number of samples ranges from 1 to 12 specimens. Furthermore, high variability between patients, with several patients with an undetermined number of tissue samples, can be observed.

Regarding the number of tissue samples, those series with a high and standard number, as in that reported by Chibbaro et al., reached the histologic diagnosis in all cases, and in a large series reported by Ahmed et al., with a high variability in the number of tissue samples, the negative histologic diagnosis rate was 16%. Despite the fact that comparison between these studies is impossible because of their methodological differences, increasing the number of samples, among other measures, could reduce sample error, as Ahmed et al. themselves proposed.

The histologic analysis of the samples taken in this case showed a yolk-sac tumor component in just 2 of 15 specimens, less than 15% of the tissue samples, thus indicating the importance of increasing the number of samples typically taken. Furthermore, the procedure for obtaining the samples is not standardized, leading to difficulties in the consistency of the diagnosis and comparison between series. Standardized histologic mapping of the tumor, as performed in the case presented, could be an effective way of reducing the impact of these issues.

CONCLUSIONS

The supraorbital frontal endoscopic approach allows the surgeon to perform histologic mapping of pineal region tumors. This technique enables standardization of the procedure used to obtain the specimens, resulting in more representative samples. This approach could result in a more accurate diagnosis, especially in mixed germ cell neoplasms.

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