Intraoperative Germinoma Staining: A Technical Note

Emanuil Naydenov[1] Petar Karazapryanov[1] Velislav Pavlov[1] Dimitar Metodiev[2] Krasimir Minkin[1]

[1] Department of Neurosurgery, University Hospital "St. Ivan Rilski," Sofia, Bulgaria
[2] Department of Neuropathology, University Hospital "St. Ivan Rilski," Sofia, Bulgaria

Address for correspondence Emanuil Naydenov, Department of Neurosurgery, University Hospital "St. Ivan Rilski,", Sofia Bulgaria (e-mail: emanuilis@abv.bg).

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Abstract

As the main treatment modality of central neural system germinomas is radiotherapy and/or chemotherapy, the exact initial diagnosis of the disease is crucial. Depending on the different national protocols, histologic verification can be obligatory in some instances. This is a serious challenge, taking into account the usual location and nonspecific macroscopic appearance of these lesions. Here, we propose a safe and effective method of intraoperative tumor enhancement that can increase the confidence of the surgeon during the intervention.

Keywords
- germinoma
- intraoperative enhancement
- fluorescein sodium

Introduction

Germinomas are the most common type of intracranial germ cell tumors (GCTs) with a peak incidence between 15 and 19 years of age.[1] They are more prevalent in males, affecting predominantly the suprasellar or the pineal gland regions. In 6 to 13% of the cases, simultaneous involvement of both of these areas can be seen.[2] The symptoms depend on the location and may include headache, vomiting, fatigue, behavioral changes, visual disturbances, and diabetes insipidus.[3] According to the different national protocols, the diagnosis of germinoma can be made by magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis.[4] However, in some instances, a histologic verification might also be required, making the operative procedure inevitable.[5]

Case Description

A 21-year-old male patient was presented to our institution with a 1-month history of headache, memory disturbance, and polydipsia. Computed tomography (CT) and MRI were performed, which revealed multifocal lesions involving both the suprasellar and pineal regions (►**Fig. 1**). Because of this pattern, central nervous system (CNS) germinoma was proposed as the most likely diagnosis. However, the accepted treatment protocol hindered us to refer the patient directly to radiotherapy. A surgical intervention was proposed because of the need of tissue sampling. Under general anesthesia, right-sided pterional craniotomy was performed. After proximal dissection of the sylvian fissure, the suprasellar region was reached via the subfrontal approach. The portion of the lamina terminalis (LT) and optic chiasm did not look suspicious. We decided to implement an intravenous contrast enhancement by using 20 mg of fluorescein sodium (FNa) per kilogram of body weight following Shinoda's protocol. No adverse effects were noted, except marked coloring of the patient's skin and urine. In the next 10 minutes, a limited region of the LT gradually turned yellow, as well as the underlying tumor mass (►**Fig. 2**). The colored lesion was partially excised without additional deterioration. A typical pattern of germinoma was demonstrated on histologic examination (►**Fig. 3**). No complica-

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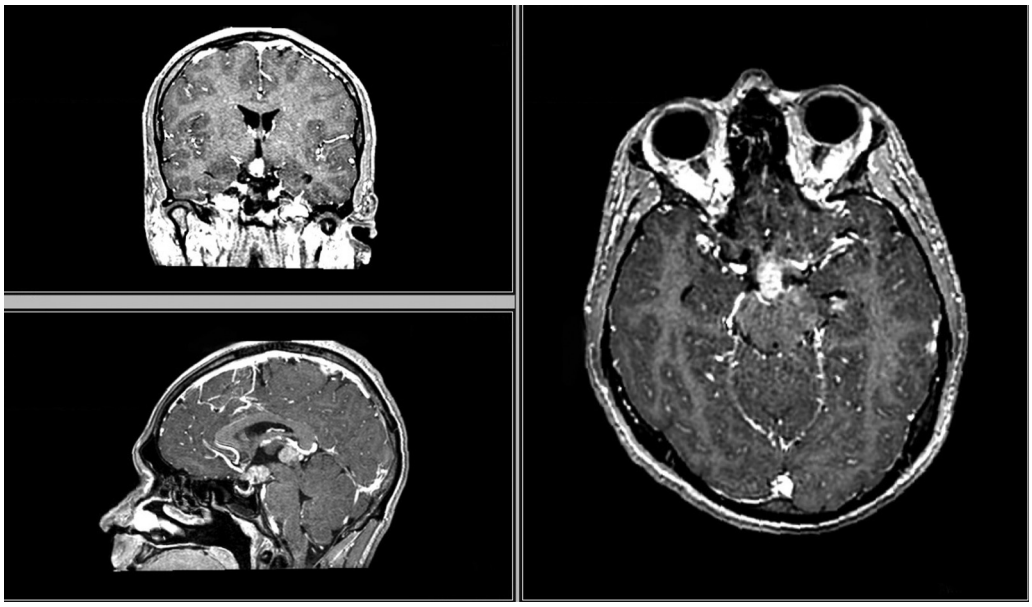

Fig. 1 The magnetic resonance imaging (MRI) demonstrated contrast-enhancing lesions involving both suprasellar and pineal gland regions.

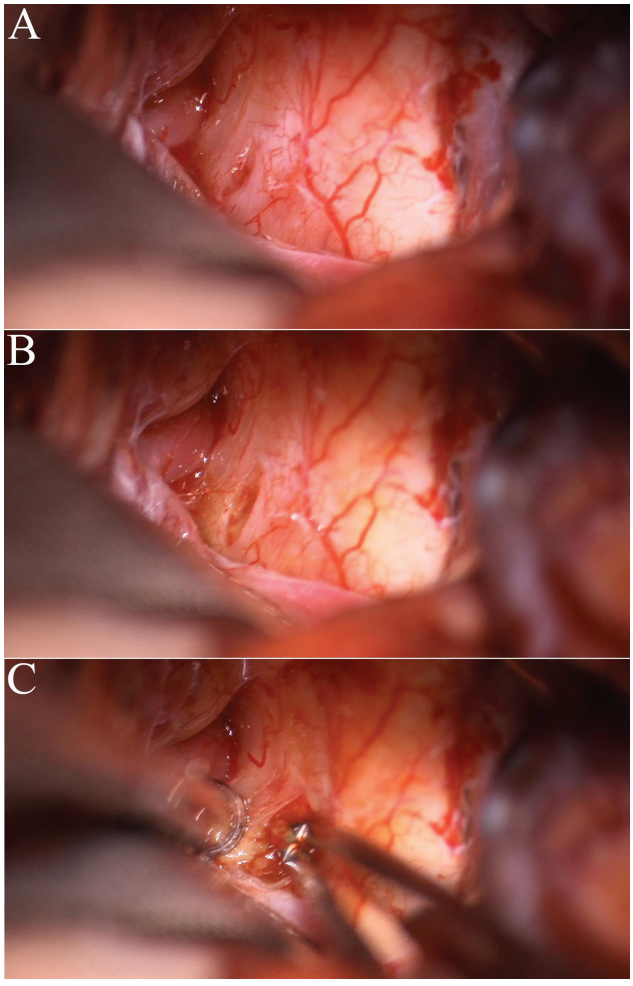

Fig. 2 The intraoperative view of lamina terminalis (LT): (**A**) native and (**B, C**) 10 minutes after the intravenous application of a high-dose fluorescein sodium (FNa).

tions were found on the early CT scan performed (►**Fig. 4**). The postoperative stay was uneventful and the patient was discharged on the fourth day after the intervention.

Discussion

Because of the high radio- and chemosensitivity, the place of surgical treatment in cases with CNS germinoma is limited, mainly to patients with symptomatic CSF occlusion.[4,5] In patients with α-fetoprotein and β-human chorionic gonadotropin elevation, biopsy could potentially be avoided.[4] However, negative or inconclusive tumor markers would be a definite indication for tissue sampling.[5] In our case, the neuroimaging studies revealed a typical pattern of multifocal CNS germinoma without CSF occlusion. The accepted treatment protocol hindered us from referring the patient directly to radiotherapy, even if the biochemical results were indicative. Therefore, an open biopsy was proposed.

In general, the CNS germinomas are involving the deep midline brain structures, thus making the surgery very complex.[5,6] We decided to obtain an open tissue sampling from the suprasellar region of the patient. The LT was accessed using a right-sided subfrontal approach. As expected, the area did not look macroscopically suspicious for any underlying lesion.

Frameless navigation has been long established as a technology with a broad potential for neurosurgical applications, but it remains expensive and sophisticated.[7] However, it cannot substitute completely the need of basic anatomical knowledge and surgical experience. In this particular case, we preferred to use the classical approach with an incision of LT according to its anatomical landmarks.

Since 1948, when the intraoperative enhancement of brain tumors was applied for the first time, a number of

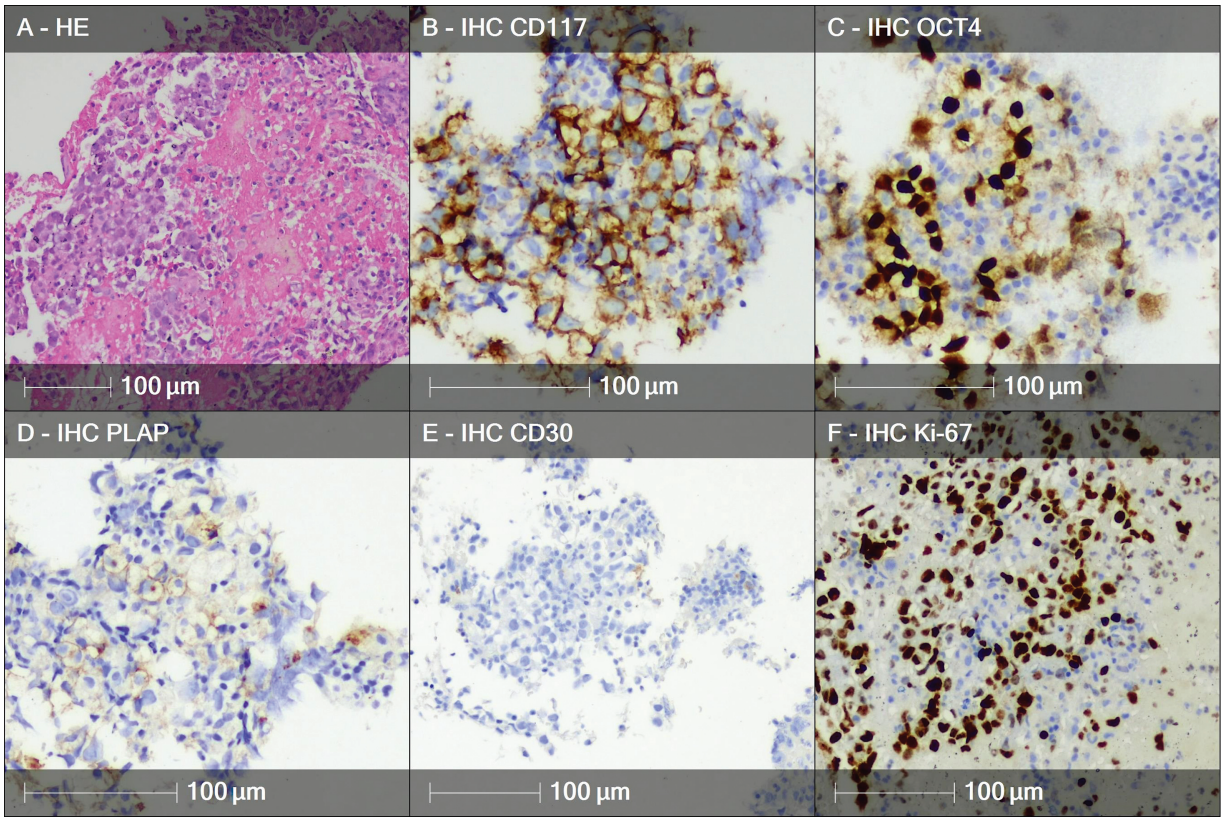

Fig. 3 The histologic examination demonstrated a typical pattern of germinoma: (**A**) large atypical cells with abundant pale eosinophilic cytoplasm, and large round nuclei with vesicular features and prominent nucleoli (hematoxylin and eosin [HE]); (**B**) positive reaction with CD117/c-kit marker in the neoplastic cells (immunohistochemistry [IHC]); (**C**) nuclear staining in the tumor cells with OCT4 marker (IHC); (**D**) PLAP immunopositive tumor cells (IHC); (**E**) negative reaction with the marker CD30 (IHC); (**F**) K67, high proliferative index (IHC).

studies were conducted to determine the relevance of this concept in neurosurgery.[8] According to Shinoda et al, the use of high-dose FNa may provide 100% of gross total resections (GTRs) in patients assigned to stage I of glioblastoma multiforme.[9] In 2006, Stummer et al completed a randomized controlled trial comparing resection of malignant glioma using 5-aminolevulinic acid (5-ALA) versus resection under standard white light microscope. The authors found that GTR was achieved in 90% of cases receiving 5-ALA compared to 36% of those in the control group.[10] Both studies concluded that intraoperative tumor staining is safe and can be successfully used for distinguishing the pathologic tissue from the normal brain structures. Hence, the application of this method allows for lowering the risk of clinical deterioration and increases the chance for a precise biopsy, which is crucial for the exact histologic diagnosis.

Fig. 4 The postoperative computed tomography (CT) scan demonstrated no data of surgical complications.

For the first time, in 2017 Takeda et al described two patients with CNS germinoma in whom 5-ALA was administered before surgical intervention. Both cases had a tumor in the pineal region that was associated with hydrocephalus, requiring endoscopic third ventriculostomy completed with a biopsy. The authors found marked and weak red fluorescence, respectively, in a 22-year-old patient and a 16-year-old patient.[11] Later on, in 2019 Ji et al described another two cases of CNS germinoma in which 5-ALA was used. Here, on the contrary, the authors were not able to detect any fluorescence during the surgery.[12]

Despite a detailed literature review, we did not find any description of the use of FNa in cases of CNS germinoma. Considering our personal experience, this method can be successfully applied in such patients, giving the operator additional confidence without the need of any special training or surgical equipment.

Conclusion

Intraoperative staining with high-dose FNa is a safe and feasible procedure in the cases with CNS germinoma. Further studies on a large number of patients are needed to confirm our data.

Ethical Approval

This study protocol was reviewed and approved by the Ethical Committee of University Hospital St. Ivan Rilski.

Authors' Contribution

All the authors had substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; participated in drafting the work or reviewing it critically for important intellectual content; approved the final version of the manuscript; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The authors confirm their contribution to the final version of the article as follows: study conception and design: E.N.; data collection: E.N. and P.K.; interpretation of results: E.N., D.M., and K.M.; draft manuscript preparation: E.N. and V.P. All the authors reviewed the results and approved the final version of the manuscript.

Patient Consent

Informed written consent was obtained from the participant in the study.

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Conflict of Interest

None declared.

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