Craniopharyngiomas are histologically benign and slow-growing lesions which originate from the embryonic remnants of squamous cells through the hypophyseal–pharyngeal duct. They are the most common non-glial tumors in childhood.\(^1\) In children, the adamantinomatous variant is prevalent and 90% of tumors have cystic characteristic.\(^2\)

Due to the location of the tumor, with variable involvement of the pituitary stalk, gland, hypothalamus, optic nerves and chiasm, complete removal with preservation of all endocrine and visual function is achieved in a small number of cases.\(^3,4\) Furthermore, even after complete macroscopic resection, the recurrence rate ranges from 23 to 50%.\(^5\)

**ABSTRACT** Craniopharyngiomas are challenging lesions to resect completely and safely due to neighbouring on the critical neurovascular structures. Intracystic interferon alpha (IFNα) chemotherapy had been used as an alternative treatment for predominantly cystic craniopharyngiomas in a limited number of patients. In this report, we presented a case of a huge cystic craniopharyngioma managed with the intracavitary IFNα application. Following the three treatment cycles, increased calcification on the solid portion of the tumor with the significantly reduction of tumor volume were observed. To our knowledge, such a this finding following the intracystic treatment with IFNα has not been reported in the literature. Further reported series and long-term follow-up could reveal whether this therapeutic option provides a definitive tumor control particularly in patients with developing calcification during the treatment.

**Key Words:** Craniopharyngioma; interferon-alpha; magnetic resonance imaging


**Anatür Kelimeleyer:** Kraniofarinjiyom; interferon-alfa; manyetik rezonans görüntüleme

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Cyst Wall Calcification Following Intracavitary Alpha Interferon Chemotherapy for a Huge Cystic Craniopharyngioma in a Child: Case Report

Dev Kistik Kraniofarinjiyomlu Bir Çocukta İntrakaviter Alfa İ Interferon Kemoterapisi Sonrası Kist Duvarı Kalsifikasyonu

Ethem GÖKSU,a Saim KAZAN,a Nursah EKER,b Volkan HAZAR,b Recai TUNCERª

Departments of
aNeurosurgery,
bPediatric Oncology,
Akdeniz University Faculty of Medicine, Antalya

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Yazışma Adresi/Correspondence:
Ethem GÖKSU
Akdeniz University Faculty of Medicine, Department of Neurosurgery, Antalya, TÜRKİYE/TURKEY
etemgoksu@mynet.com

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To achieve the tumor control and improved length of survival, while maintaining quality of life, less invasive procedures have been considered for predominantly cystic lesions in children. Intracystic interferon alpha (IFNα) chemotherapy has been used as an alternative treatment since the first report of Cavalheiro et al. in 2005. In this report, we presented a case of a huge cystic craniopharyngioma managed with the intracavitary IFNα application. Following the three treatment cycles, increased calcification on the solid portion of the tumor with the significantly reduction of tumor volume were observed. To our knowledge, such a finding following the intracystic treatment with IFNα has not been reported in the literature.

CASE REPORT

PRESENTATION AND EXAMINATION
This 4-year-old girl was admitted with the first attack of focal clonic seizure on her left arm and leg. Neurologic examination revealed the slight left hemiparesis and bilateral papilledema. Her physical and psychomotor development were normal and no endocrine deficiency was detected. Computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated a multilobulated, cystic and calcified lesion (Figure 1A, B, C). Estimated tumor volume was calculated as 170 cm³ using three largest axes multiplied by a correction factor of 0.52.

PREOPERATIVE PROCEDURES, OPERATION AND DRUG APPLICATION
The parents of the child were informed about the procedure. In addition, a private permission was requested for “the use of the drugs without their routine application” from the Ministry of Health, Republic of Turkey. In the operation, a silicone catheter was inserted to the cyst cavity by direct puncture through an orifice in the right frontal trepanation and connected to an Ommaya reservoir. In every application, a 18 gauged branule was installed into the reservoir with the aim of spontaneous drainage of the cyst fluid. When the flow discontinued or the patient began to complain of a headache, branule was removed and one milliliter (ml) IFNα2A was injected. Each application consisted of an injection of 3 000 000 units of IFNα2A, totaling 36 000 000 units, which was considered one treatment cycle.

POSTPROCEDURAL COURSE
Control MRI was performed at one, three and six months after the initial application. MR images following one cycle of treatment demonstrated the significantly shrinkage of the cystic tumor. Estimated tumor volume was calculated as 44.5 cm³ (Figure 2 A, B). After the three treatment cycles, dimensions of the lesion were similar on MR images. However, CT scan exhibits the apparent cyst wall calcification and also increase the calcified portion of the lesion (Figure 2C). During the treatment protocol drug was well-tolerated and no significant side effect developed. Papilledema regressed, no seizure and no new endocrine deficit were detected.

DISCUSSION
In our reported case, we observed the major reduction of tumor volume (a decrease of 75%) and transforming the fluid intensity to CSF-like appea...

FIGURE 1: Initial axial NECT (A), axial (B) and sagittal (C) T1W MR images shows a multilobulated, predominantly cystic including hyperdense proteinaceous fluid and partially calcified tumor.

FIGURE 2: Axial (A), sagittal (B) T1W MR images demonstrates the significantly shrinkage of the cystic tumor and CSF-like fluid intensity after the one cycle of treatment. Axial NECT scan (C) exhibits the apparent cyst wall calcification and also increase the calcified portion of the lesion (arrows) following three cycles of treatment. C: catheter.
rance on MR images after the first cycle of protocol. But interestingly, after the three cycles of treatment, CT scans demonstrated the increased calcification on the solid portion of the tumor. Calcification reflects a benign nature of any tumor in which tumoral cells are in a quiescent or dormant state. In craniopharyngiomas, this part of the tumor may have not the features of proliferation or active secretion. We believe that tumor calcification as a treatment response might be interpreted with the most desirable result of a drug-tumor interaction.

Interferons (IFNs) are glycoproteins which are responsible for the control of cell differentiation and proliferation.\(^7\) IFNa is the first cytokine produced by a DNA recombinant technique that is effective against cancer.\(^8\) It is used therapeutically for its properties of inducing an “antiviral” state in cells, inhibiting cellular proliferation, and creating immunomodulation. As a chemotherapeutic agent, IFNa is usually given for the treatment of squamous cells carcinoma. In the past, postoperative intracavitary IFNa had been used in patients with malignant glioma.\(^9\) In addition, systemic IFNa has induced objective responses in children with recurrent craniopharyngioma, anaplastic astrocytoma, brainstem glioma, and cerebral primitive neuroectodermal tumor, and in adults with newly diagnosed low-grade astrocytoma.\(^10,11\) However, major limitations of its systemic application included hematological, hepatic, and neurological complications. Recently, Yeung et al. reported the significant and durable responses of weekly subcutaneous pegylated IFNa application in 5 children with recurrent craniopharyngiomas without untolerable side effects.\(^12\)

Intracavitary use of IFNa in cystic craniopharyngioma was firstly reported by Cavalheiro et al. in 2005.\(^6\) In this report, they presented the successful results of nine cases in a mean follow-up of 1 year and 8 months. In 2010, a multicenter study of 60 pediatric patients revealed the clinical and radiological improvement in 76% of the cases in an average follow-up duration of 44 months.\(^13\)

IFNa applications are carried out via an Ommaya reservoir connected to a silicone catheter. Intratumoral catheter could be placed to the cyst cavity in various ways such as; frontal craniotomy and subfrontal microsurgical access, neuroendoscopic transventricular fenestration of the cyst or direct frontal puncture for extensive lesions. Authors considered disease to be controlled when a tumor decreased more than 50%. Beside the reduction of tumor volume, cyst fluid appeared the cerebrospinal fluid (CSF) intensity on magnetic resonance (MR) images. They applied one to nine cycles per patient depending on the clinical or radiological response of the tumor. In 30% of patients, some kind of side effects such as headache, fever, palpebral edema, chronic fatigue syndrome and arthritis were described. However, none of them required the discontinuation of treatment.\(^13\) The major advantage of IFNa is to be nonneurotoxic and does not appear any significant complication even if it spills into the subarachnoid space. It was also emphasized that tumor was less adherent than a typical craniopharyngioma after IFNa treatment, making resection easier (unlike bleomycin).\(^6\)

The cystic component of craniopharyngioma are possibly the result of an active production of the fluid by the epithelial cells of tumor.\(^14-16\) This portion of the tumor is associated to a major risk of recurrence in spite of the presence of benign histological features, thus suggesting a proliferative mechanism in its formation and growth. Mechanical action of withdrawing the intratumoral liquid in every application could be one of the mechanisms of the decrease in tumor volume with IFNa treatment. But more importantly, IFNa may have direct and indirect effects on tumoral cells with anti-proliferative, pro-apoptotic, anti-angiogenetic and immunomodulatory properties.\(^17,18\)

In conclusion, intracystic IFNa treatment has been considered as an efficacious, safe, easy to handle, inexpensive and less invasive modality for predominantly cystic craniopharyngiomas. Tumor calcification may demonstrate with the good treatment response but further reported series and long-term follow-up are needed to reveal the association of tumor calcification and recurrence following intracystic treatment with IFNa. In addition, drug-tumor interaction, individual differences in treatment response and changing the characteristics of the lesion during the applications are worth the topics to further research.
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