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

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

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ABSTRACT Craniopharyngiomas are challenging lesions to resect completely and safely due to neighbouring on the critical neurovascular structures. Intracystic interferon alpha (IFNα) chemotheraphy 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

ÖZET Kraniofarinjiyomlar kritik nöral ve damarsal yapılarla yakın ilişkisi nedeniyle tam ve güvenli rezeksiyonları güç lezyonlardır. Kist içi interferon alfa (IFNα) kemoterapisi, çoğunluğu kistik tümörlerde alternatif bir tedavi yöntemi olarak sınırlı bir hasta grubunda kullanılmıştır. Bu yazıda, kist içi IFNα ile tedavi edilen dev kistik kraniofarinjiyomalı bir olguyu sunduk. Üç tedavi döngüsü sonrası kist hacminde belirgin azalmayla birlikte tümörün solid bölümünde kalsifikasyon artışı gözlendi. Bilgilerimize göre, kist içi IFNα tedavisi sonrası böyle bir bulgu şimdiye dek literatürde bildirilmemiştir. Daha geniş seriler ve uzun takipler bu tedavi seçeneğinin, özellikle tedavi sırasında kalsifikasyon gelişen olgularda kalıcı bir tümör kontrolü sağlayıp, sağlamayacağını ortaya koyabilir.

Anahtar Kelimeler: Kraniofarinjiyom; interferon-alfa; manyetik rezonans görüntüleme

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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]

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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) chemotheraphy has been used as an alternative treatment since the first report of Cavalheiro et al. in 2005.[6] 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.

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 sligth 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 cm^3 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 additon, 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 cm^3 (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-

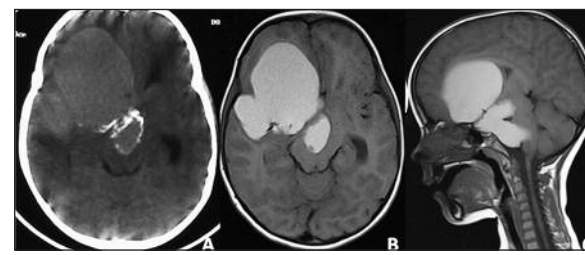

FIGURE 1: Initial axial NECT **(A)**, axial **(B)** and sagittal **(C)** T1W MR images shows a multilobulated, predominantly cystic including hyperdense proteinaceous fluid and partially calcified tumor.

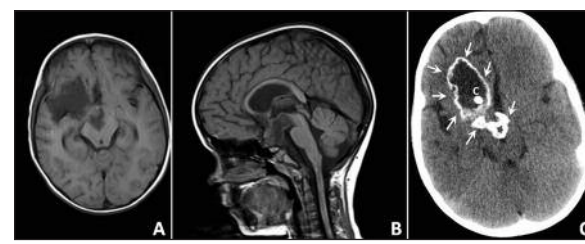

FIGURE 2: Axial **(A)**, sagittal **(B)** T1W MR images demonstrates the significantly shrinkage of the cystic tumor and CSF-like fluid intensity after the one cycle of treatment. Axial NECT scan **(C)** exhibits the apparent cyst wall calcification and also increase the calcified portion of the lesion (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 migth 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] IFNα 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 chemotherapic agent, IFNα is usually given for the treatment of squamous cells carcinoma. In the past, postoperative intracavitary IFNα had been used in patients with malignant glioma.[9] In addition, systemic IFNα 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 IFNα application in 5 children with recurrent craniopharyngiomas without untolerable side effects.[12]

Intracavitary use of IFNα in cystic craniopharygiomas was firstly reported by Cavalheiro et al. in 2005.[6] In this report, they presented the succesful 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]

IFNα 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 IFNα 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 IFNα treatment, making resection easier (unlike bleomycine).[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 IFNα treatment. But more importantly, IFNα may have direct and indirect effects on tumoral cells with anti-proliferative, pro-apoptotic, anti-angiogenetic and immunomodulatory properties.[17,18]

In conclusion, intracystic IFNα 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 IFNα. 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.

REFERENCES

1. Al-Mefty O, Hassounah M, Weaver P, Sakati N, Jinkins JR, Fox JL. Microsurgery for giant craniopharyngiomas in children. Neurosurgery 1985;17(4):585-95.
2. Marchal JC, Klein O, Thouvenot P, Bernier V, Moret C, Chastagner P. Individualized treatment of craniopharyngioma in children: ways and means. Childs Nerv Syst 2005;21(8-9): 655-9.
3. Elliott RE, Moshel YA, Wisoff JH. Minimal residual calcification and recurrence after gross-total resection of craniopharyngioma in children. J Neurosurg Pediatr 2009;3(4):276-83.
4. Elliott RE, Wisoff JH. Successful surgical treatment of craniopharyngioma in very young children. J Neurosurg Pediatr 2009;3(5):397-406.
5. Tomita T, Bowman RM. Craniopharyngiomas in children: surgical experience at Children's Memorial Hospital. Childs Nerv Syst 2005; 21(8-9):729-46.
6. Cavalheiro S, Dastoli PA, Silva NS, Toledo S, Lederman H, da Silva MC. Use of interferon alpha in intratumoral chemotherapy for cystic craniopharyngioma. Childs Nerv Syst 2005; 21(8-9):719-24.
7. Tagliaferri P, Caraglia M, Budillon A, Marra M, Vitale G, Viscomi C, et al. New pharmacokinetic and pharmacodynamic tools for interferon-alpha (IFN-alpha) treatment of human cancer. Cancer Immunol Immunother 2005; 54(1):1-10.
8. Chawla-Sarkar M, Lindner DJ, Liu YF, Williams BR, Sen GC, Silverman RH, et al. Apoptosis and interferons: role of interferon-stimulated genes as mediators of apoptosis. Apoptosis 2003;8(3):237-49.
9. Maleci A, Antonelli G, Guidetti B, Dianzani F. Pharmacokinetics of recombinant interferon-alpha 2 following intralesional administration in malignant glioma patients. J Interferon Res 1987;7(1):107-9.
10. Jakacki RI, Cohen BH, Jamison C, Mathews VP, Arenson E, Longee DC, et al. Phase II evaluation of interferon-alpha-2a for progressive or recurrent craniopharyngiomas. J Neurosurg 2000;92(2):255-60.
11. Watanabe T, Katayama Y, Yoshino A, Komine C, Yokoyama T, Fukushima T. Treatment of low-grade diffuse astrocytomas by surgery and human fibroblast interferon without radiation therapy. J Neurooncol 2003;61(2):171-6.
12. Yeung JT, Pollack IF, Panigrahy A, Jakacki RI. Pegylated interferon-α-2b for children with recurrent craniopharyngioma. J Neurosurg Pediatr 2012;10(6):498-503.
13. Cavalheiro S, Di Rocco C, Valenzuela S, Dastoli PA, Tamburrini G, Massimi L, et al. Craniopharyngiomas: intratumoral chemotherapy with interferon-alpha: a multicenter preliminary study with 60 cases. Neurosurg Focus 2010; 28(4):E12.
14. Arefyeva IA, Semenova JB, Zubairaev MS, Kondrasheva EA, Moshkin AV. Analysis of fluid in craniopharyngioma-related cysts in children: proteins, lactate and pH. Acta Neurochir (Wien) 2002;144(6):551-4; discussion 554.
15. Honegger J, Renner C, Fahlbusch R, Adams EF. Progesterone receptor gene expression in craniopharyngiomas and evidence for biological activity. Neurosurgery 1997;41(6): 1359-63; discussion 1363-4.
16. Szeifert GT, Julow J, Szabolcs M, Slowik F, Bálint K, Pásztor E. Secretory component of cystic craniopharyngiomas: a mucino-histochemical and electron-microscopic study. Surg Neurol 1991;36(4):286-93.
17. Ierardi DF, Fernandes MJ, Silva IR, Thomazini-Gouveia J, Silva NS, Dastoli P, et al. Apoptosis in alpha interferon (IFN-alpha) intratumoral chemotherapy for cystic craniopharyngiomas. Childs Nerv Syst 2007;23(9): 1041-6.
18. Ferrantini M, Capone I, Belardelli F. Interferon-alpha and cancer: mechanisms of action and new perspectives of clinical use. Biochimie 2007;89(6-7):884-93.