Intracystic interferon- α treatment leads to neurotoxicity in craniopharyngioma: case report

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Craniopharyngioma is a benign, cystic suprasellar tumor that can be treated with intracystic chemotherapy. Interferon- α (IFN- α) has been gaining popularity as an intracystic treatment for craniopharyngioma because of its efficacy and supposed benign neurotoxicity profile. In this case report the authors describe a patient who, while receiving intracystic IFN- α , suffered a neurological event, which was believed to be related to drug leakage outside the cyst. This is the first report of a focal neurological deficit potentially attributable to intracystic IFN- α therapy, highlighting the fact that IFN- α may have neurotoxic effects on the central nervous system. Given this case and the results of a literature review, the authors suggest that a positive leak test is a relative contraindication to intracystic IFN- α treatment.

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CRANIOPHARYNGIOMA is a benign tumor thought to arise from squamous epithelial remnants of Rathke's pouch.¹² In theory, it is curable with radical resection; however, complete removal is often difficult to achieve given the lesion's suprasellar location close to the optic chiasm, pituitary stalk, hypothalamus, carotid artery, and anterior cerebral arteries. Thus, these tumors are often treated using a multimodality approach with other treatment options including biopsy, partial resection, radiotherapy, and intracystic therapies in various combinations. Intracystic therapies are often considered because cysts are a predominant feature in more than 90% of these tumors and provide a reservoir into which antineoplastic agents can be delivered.¹⁶ Interferon (IFN)- α has been gaining popularity as an intracystic therapy for craniopharyngioma as a result of its efficacy and supposed benign toxicity profile.⁴ However, in the current case report we describe a patient who, while receiving intracystic IFN- α , suffered a neurological event, which was believed to be related to drug leakage outside the cyst. It is the first report of a focal neurological deficit potentially attributable to intracystic IFN- α therapy, highlighting the fact that IFN- α may have neurotoxic effects on the central nervous system.

Case Report

History and Examination

A 7-year-old girl presented with a 2-year history of progressive, multiple daily headaches. She denied other symptoms such as nausea, vomiting, or visual changes. Her neurological exam was normal. There was no papilledema on funduscopy. Her medical history was significant only for celiac disease. She had not been on any medications and had no allergies. Birth and family history were noncontributory. Brain CT and MRI demonstrated a multicystic, partially calcified suprasellar lesion extending into the prepontine cistern and bilateral sylvian fissures (Fig. 1). There was no hydrocephalus. The presumptive diagnosis was craniopharyngioma.

Operation

It was believed that attempted resection of the tumor would have significant morbidity and that the most appropriate treatment of the tumor would be radiation therapy. Given the young age of the patient and the predominantly cystic lesion, it was decided to place a catheter attached to a subgaleal Ommaya reservoir into the left temporal cyst (the

ABBREVIATIONS IFN = interferon; SSPE = subacute sclerosing panencephalitis.

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FIG. 1. Preoperative coronal (left) and axial (right) T2-weighted MR images demonstrating a heterogeneous multicystic suprasellar lesion, in keeping with craniopharyngioma.

largest cyst) followed by IFN- α intracystic therapy. If this proved successful at reducing the size of the cyst, then the plan was to treat the other cysts similarly with the goal of delaying radiation therapy for as long as possible and keeping her neurologically intact with a good quality of life. To minimize the risk of drug leakage outside the cyst, we used a catheter with holes that extended only 8 mm from the tip instead of the standard 18 mm in a ventricular catheter.

Postoperative Course

Postoperatively, all of the cysts were smaller, indicating communication between the cysts and obviating the need to treat the other cysts independently. A leak test of the Ommaya reservoir was done 11 days after surgery (Fig. 2). Injection of 2 ml of radiopaque contrast material into the reservoir filled the cyst, with no leakage. Note, however, that contrast leakage into the subarachnoid spaces of the sylvian fissure and the medial aspect of the floor of the middle cranial fossa occurred after an additional 1.5 ml was injected. Given these results, it was decided to limit the injection volume of IFN- α to 1.5 ml.

Intracystic IFN- α injections began on postoperative Day 13 with a planned regimen of 3 million IU 3 days a week for 4 weeks' duration (12 doses total). Treatments involved the aspiration of cyst fluid followed by injection of 1.5 ml of drug. Aspiration volumes varied from 0.5 to 13 ml. On the 12th treatment, the patient experienced 3

FIG. 2. Leak test. Coronal CTs showing filling of the cysts after the injection of 2 ml of contrast (left) and after an additional 1.5 ml of contrast was injected (right). Note the leakage of contrast into the subarachnoid space (arrow). Asterisks indicate contrast within the cyst.

FIG. 3. Coronal T2-weighted MR image obtained after an acute neurological event, demonstrating a T2 signal change in the operculum. The area of signal change is around the site where the catheter punctured the cyst wall, suggesting that it is related to fluid leakage from within the cyst.

episodes of transient right leg sensory changes. Two days later, she experienced a frontal headache associated with expressive aphasia, pallor, and sensory changes in her right leg. These symptoms lasted 7 hours then resolved spontaneously. She did not have any visual changes or altered mental status. Her neurological exam was unremarkable upon presentation to the hospital. Obtained MRI studies demonstrated an area of T2 hyperintensity in the white matter adjacent to where the cyst wall was punctured by the catheter (Fig. 3). The catheter was in a good position. There was no restricted diffusion to suggest an infarct. The cysts were smaller, and the solid component of the tumor remained stable in size. Electroencephalography did not reveal epileptiform activity. The patient was discharged home in excellent condition; however, given concerns that her transient symptoms were related to the IFN- α , her treatments were stopped.

The child remained neurologically intact with no residual deficits from her acute neurological event. Follow-up MRI 1 month after the cessation of IFN- α treatments showed decreased edema around the catheter and a reduction in cyst size (Fig. 4). Systemic pegylated IFN- α was administered weekly by subcutaneous injection. She tolerated these treatments well, with only mild side effects of fatigue and decreased energy. After 7 months of this therapy, she complained of more headaches, nausea, and mood changes. Although there was no growth in the solid component of the tumor, both the third ventricular and left temporal cysts were larger on MRI, and hydrocephalus was developing because the foramina of Monro were obstructed by an enlarged third ventricular cyst. Because the treatment was ineffective at controlling the size of the cysts, the pegylated IFN- α was discontinued. The third ventricular cyst was fenestrated endoscopically, and an Ommaya reservoir was left in place. At the time of her last follow-up, 2 weeks after

FIG. 4. Coronal T2-weighted MR image obtained 1 month after an acute neurological event, demonstrating the resolution of signal change.

surgery, the patient's headaches and mood had improved and her CT scan showed decompression of the third ventricular cyst and resolution of the hydrocephalus. The plan is to repeat her imaging in 3 months to ensure that the cyst does not reaccumulate fluid. If the cyst does reaccumulate fluid, we would consider intracystic IFN- α treatments as long as the leak test was negative.

Discussion

Bleomycin was the first chemotherapeutic drug to be used intracystically for craniopharyngioma. Despite its documented efficacy, it is neurotoxic and can cause severe neurological complications such as blindness, decreased level of consciousness, hypothalamic injury, seizures, hemiparesis, and even death.^{2,9} Interferon- α has become an attractive alternative with similar effectiveness but without severe neurotoxicity.^{3,4,10} This drug is believed to act through the Fas-mediated apoptotic pathway but also has immunomodulatory, antiproliferative, and antiangiogenic activities.¹⁰ The standard dose is 3 million IU injected every other day (3 times a week) for 4 weeks.⁴

Patients often receive several cycles of therapy, depending on their response to treatment. Before injecting the medication, a contrast injection test is done after the catheter is implanted to determine if any leakage is present. However, the presence of leakage is not considered a contraindication to treatment as several studies have reported only mild side effects from IFN- α when injected intrathecally, intraventricularly, or directly into a tumor for carcinomatous meningitis, encephalitis, or intracranial malignancies.^{4–6,14}

Most reported side effects of intracystic IFN- α have been mild.⁴ In the largest multicenter prospective study with 60 patients, the side effects of headache, palpebral edema, and fever were present in approximately 30% of the patients, but none were severe enough to stop treat-

ment.⁴ A minority of patients reported chronic fatigue syndrome and arthritis.

Despite these seemingly reassuring results, there is some evidence that IFN- α has the potential to be neurotoxic, particularly if it distributes into the ventricular system. The drug has been used intrathecally for the treatment of neoplastic meningitis where side effects of transient chemical arachnoiditis and chronic fatigue were found to occur in 73% and 91% of patients, respectively.⁵ Intraventricular IFN- α has been safely used in the treatment of other diseases, such as subacute sclerosing panencephalitis (SSPE), with the only reported side effect being hyperpyrexia.⁶ However, significant neurotoxic side effects have been observed with intraventricular IFN- α delivery. In a Phase II trial conducted by Meyers et al. in 1991, 9 patients with leptomenigeal disease were treated with intraventricular IFN- α at doses of 3–9 million IU administered 3 times per week, which is up to triple the dose used for intracystic treatment in craniopharyngiomas. Severe neurotoxicity was observed in 7 of the 9 patients, manifesting as a progressive vegetative state that initially presented as confusion and expressive dysphasia. These symptoms progressed to aphasia and various degrees of unresponsiveness over a few days. After stopping treatment, 2 patients died and those who recovered took an average of 17 days to become verbally responsive and oriented. Other observed neurotoxic side effects were impaired cognition, parkinsonism, hearing loss, seizures, hiccups, nausea and vomiting, and encephalopathy. Interestingly, the patients with severe neurotoxicity had previously received brain radiation, whereas the 2 patients who had not had radiation experienced only mild side effects.

Another case report in which intraventricular IFN- α was used for SSPE describes a neurological deterioration with akinetic mutism after 1 week of intraventricular therapy, despite CSF analysis showing a decrease in viral RNA.⁸ But because the patient in that case initially presented with decreased responsiveness and dysphasia, it is difficult to say whether the neurological deterioration was attributable to progression of the underlying disease or the IFN- α therapy.

Further evidence of the neurotoxicity of intraventricular IFN- α was published in a case report of an 8-year-old boy who had received a standard treatment regimen of 3 million IU of intracystic IFN- α 3 times a week after a contrast injection test clearly demonstrated intraventricular leakage.¹³ Craniopharyngioma had been diagnosed in this patient when he was 8 months of age, and he underwent radiation (54 Gy) at 3 years of age after 3 subtotal resections for recurrent disease. Severe brain atrophy and hydrocephalus developed 2 weeks after completion of a standard 4-week cycle of intracystic IFN- α therapy.¹³ The fact that the patient had previously received radiation again raises the question of whether radiation may potentiate the neurotoxic effects of IFN- α .

In our patient, it seems most likely that her transient expressive aphasia occurred from IFN- α leakage from the cyst into adjacent brain parenchyma. This is supported by the fact that the T2 signal change demonstrated in her operculum on MRI was located circumferentially around the point where the catheter punctured the cyst. Similar radio-

logical changes have also been seen with bleomycin leakage.¹¹ It remains unclear why our patient became symptomatic after her 12th treatment, although bleomycin toxicity has been documented at a similar time point.¹¹ It is possible for the holes in the catheter to become exposed as the cyst collapses, but this seems unlikely since the cyst had not changed significantly in size when the aphasic event occurred and the catheter remained deep enough to the cyst surface that the catheter holes would have remained well within the cyst. The last 3 treatments involved the aspiration of larger volumes of cyst fluid (10–13 ml per treatment) compared with the earlier treatments. Although aspiration of these volumes is well within the 20 ml maximum in Cavalheiro's protocol, perhaps larger volume changes in the cyst increased the permeability around the catheter.⁴

Interferon- α -related neurotoxicity could be caused by an inflammatory reaction in brain parenchyma exposed to the drug. Interferon- α has immunomodulatory properties. When administered systemically, it triggers an inflammatory response leading to the release of inflammatory cytokines, such as tumor necrosis factor- α , interleukin-1, and interleukin-6.¹⁵ In the central nervous system, IFN- α induces prostaglandin- E_2 .¹⁵ A transgenic mouse model has been developed by Akwa et al. to study the effect of astrocyte-targeted expression of IFN- α .¹ In these mice, astrocyte-specific expression of IFN- α led to inflammation and neurodegeneration manifesting as a progressive inflammatory encephalopathy. Interestingly, many of the changes seen in these mice closely resemble Aicardi-Goutières syndrome, a rare type of familial encephalopathy characterized by severe and progressive brain atrophy and high levels of IFN- α in CSF.⁷ The changes on MRI described in the present case report are in keeping with an inflammatory reaction in the brain parenchyma surrounding the catheter where it punctured the cyst. It is possible that the cerebral edema was responsible for the neurological deficit or that the inflammation caused a focal seizure that was not captured on postictal electroencephalography.

Conclusions

Contrary to the belief that IFN- α is not neurotoxic, this case report demonstrates that exposure of brain parenchyma to IFN- α can lead to focal neurological deficits with radiological changes on MRI. Both the neurological deficit and the T2 abnormality were reversible in our patient, which suggests that the cessation of therapy is an effective management strategy for this problem. According to a review of the literature, intraventricular IFN- α seems to have the potential to cause neurological deficits, especially after prior radiation to the brain. Considering our case and the literature review, we suggest that a positive leak test is a relative contraindication to intracystic IFN- α treatment, particularly if the patient has previously received radiation.

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Author Contributions

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