Intratumoural bleomycin as a treatment for recurrent cystic craniopharyngioma.  
Case report and review of the literature

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Summary

Introduction. The majority of craniopharyngioma (CF) have a cystic component and only 10% are completely solid. In tumors with a large cystic component, stereotactic drainage or instillation of radioactive and/or chemotherapeutic agents have been used. Only several authors have reported the use of bleomycin for the treatment of cystic CF.

Case report. The authors present the case of a nineteen years old patient with a recurrent cystic CF who was treated with intratumoral injections of bleomycin. The patient had been operated on three times before because of regrowth of the tumor. This last time he had a severe disturbance of his visual acuity and a huge regrowth of the cystic CF. An intracystic catheter stereotactically placed was connected to an Ommaya reservoir and, after assuring the impermeability of the cyst, bleomycin was administered through the reservoir up to a total dose of 45mg distributed in six doses. No complications were detected during and after the procedure. A MR performed 4 months after treatment showed a clear reduction in the size of the cyst but 10 months later a new regrowth of the cyst was detected by MR with no new signs or symptoms. A total dose of 30 mg divided in six doses was administered. No complications occurred. The MR 18 months after the first treatment showed the reduction in size of the tumor. The ophthalmological study showed almost normal visual acuity in both eyes.

Discussion. Although there is not an established protocol for the indication and the form of application of intracystic bleomycin, results with this treatment for cystic CF seem good in the literature. However, the risk of local complications after the administration of intratumoural bleomycin in these patients is around 10%, and some fatal toxic reactions have been recently reported.

Conclusion. Intracystic administration of bleomycin is a valid option as adjuvant therapy for CF in patients with recurrences that are not surgical candida-

tes because of the high risk of complications. The role of bleomycin as a primary treatment for CF and treatment protocols remain to be established with additional studies.


Bleomicina intratumoral como tratamiento de un craneofaringioma quístico recidivante. Descripción de un caso y revisión de la literatura

Resumen

La mayoría de craneofaringiomas (CF) tienen un componente quístico, siendo solamente un 10% completamente sólidos. Para el tratamiento de tumores con gran componente quístico se han usado el drenaje estereotáxico o la instilación de agentes radioactivos y/o quimioterápicos. Pocos autores han publicado sobre el uso de la bleomicina para el tratamiento de CF quísticos.

Presentamos el caso de un paciente de 19 años con un CF quístico recidivado que fue tratado con inyecciones intratumorales de bleomicina. El paciente había sido intervenido en tres ocasiones por recrecimientos del tumor. Esta última vez presentaba una disminución severa de la agudeza visual y un recrecimiento gigante del CF quístico. Con ayuda de estereotaxia se le colocó un catéter intracístico conectado a un reservorio Ommaya y, tras comprobar la estanqueidad del quiste, se le administró bleomicina a través del reservorio a una dosis total de 45mg repartida en seis veces. La RM realizada 4 meses después mostraba la clara disminución en el tamaño del quiste. 14 meses después una RM mostró un nuevo recrecimiento del quiste, sin existir signos ni síntomas asociados al mismo. Se administró bleomicina a través del reservorio Ommaya a una dosis total de 30mg repartida en 6 dosis. No ocurrieron complicaciones y la RM 18 meses después del primer tratamiento mostró la clara disminución del tamaño tumoral. El estudio oftalmológico era casi normal en ambos ojos.
Aunque no existe un protocolo establecido de indicaciones y forma de aplicación de este tratamiento, los resultados de los casos reportados en la literatura parecen buenos. Sin embargo, el riesgo de complicaciones locales tras la administración de bleomicina en estos pacientes está alrededor del 10%, y recientemente se han publicado efectos tóxicos fatales.

Así pues, la administración intraquística de bleomicina es una opción válida como tratamiento adyuvante para pacientes con CF quísticos recurrentes no candidatos a cirugía por el alto riesgo de complicaciones. El papel de la bleomicina como primer tratamiento para CF y los protocolos de administración aún están por determinar con sucesivos estudios.


Introduction

Craniopharyngiomas (CF) are the most frequent non-glandular tumors in infancy, representing about 6-8% of all pediatric neoplasms. They are benign tumors that originate from remains of the escamous epithelium along the involuted duct between the hypophysis and the Rathke’s pouch, usually localized in the sellar and supra sellar region.

Treatment of CF is controversial, although the majority of authors agree on radical surgical therapy as the ideal option. However, in spite of the advances in microsurgical techniques, total resection is associated with serious complications, such as visual and endocrinological disturbances. Partial resection, with or without radiotherapy or radiosurgery, has also been used in the treatment of these lesions. However, recurrences are frequent even after radical surgery, and usually pose serious problems for patients management.

Cystic CF represent a special kind of tumor amenable to therapeutic approaches other than surgical, such as drainage by stereotactic puncture or intracavitary injection of radioactive solutions or chemotherapeutical agents. The case of a patient with a recurrent cystic CF is presented. He had been surgically operated on three occasions and received conventional radiotherapy.

The last recurrence was treated by intratumoral injection of bleomycin introduced through an Ommaya reservoir connected to an intracystic catheter implanted by using stereotactic technique.

Case report

A nineteen-year-old man was admitted to our Unit because of regrowth of previous treated CF. At the age of eight years he had been admitted to another hospital because of sleepiness, headache and blurred vision. Endocrinological study was within normal limits. A cranial CT showed a suprasellar mass compressing the third ventricle and causing hydrocephalus. A ventriculoperitoneal shunt was placed and the tumor was subtotally resected through a right frontal craniotomy. Treatment was completed with conventional radiotherapy. Following the operation the patient needed hormonal therapy because of panhypopituitarism, but physical and educational development was good. Seven and ten years later, he underwent operations with subtotal tumor resection on both occasions.

One year after the last operation he presented a regrowth of the tumor. At this time he had a panhypopituitarism and visual disturbance. Visual acuity was 0.4 in the left eye and he could just count fingers at 1 metre with the right eye. Cranial CT and MR showed tumor recurrence with a big cystic component (Figure 1). An intracystic catheter stereotactically placed was connected to an Ommaya reservoir. LDH in the cystic liquid was 256 IU/l. Five days later water soluble contrast media was injected into the cyst and serial CT scans were performed in order to prove its impermeability (Figure 2). After assuring the disappearance of the contrast from the cyst, bleomycin was administered through the Ommaya reservoir; the total dose was 45 mg distributed in six doses in twelve days. A cranial CT was performed at the end of the treatment showed a slight reduction in the size of the cyst. Intracistyic LDH at the end of the treatment was 667 IU/l.

A MR performed 4 months after the treatment showed a clear reduction in the size of the cyst (Figure 3).

After 14 months a new MR showed a smaller regrowth of the cyst (Figure 4). No new clinical signs or symptoms had appeared. A cystography again was performed and a total dose of 30 mg of bleomycin distributed in 6 doses in twelve days was administered through the Ommaya reservoir. No complications occurred during the procedure different from transient fever. LDH in the fluid was 995 IU/l at the beginning of the treatment, and 770 IU/l at the end. A MR performed 18 months after the first treatment with bleomycin showed reduction in the size of the cyst (Figure 5). The ophtalmological study showed normal visual acuity in the left eye and 0.7 in the right eye and the patient continues on substitutive hormonal therapy.

Discussion

Most appropriate therapy for CF continues to be a subject for debate among neurosurgeons. Some authors support radical surgery, which should theoretically be a definitive treatment for these tumors. However, the localisation of CF makes that very aggressive surgical therapy occasionally results in excessive morbidity. On the other hand, there
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Figure 1. Sagital (left) and axial (right) TI-weighted gadolinium-enhanced MR images obtained before the treatment. They show the huge recurrence of the bilobulated cystic tumor in the suprasellar region compressing the third ventricle.

Figure 2. Axial CT scan before (left) and after (right) the administration of radiopaque contrast through the Ommaya reservoir. Images show the impermeability of the cyst, with no contrast outside the cystic tumor.
are many cases of CF reported in the literature that recurred following apparently total excision\(^2\),\(^4\). For there reasons, other authors support less aggressive treatments at least in selected cases such as partial resection followed by radiotherapy or radiosurgery\(^5\),\(^6\).

The majority of CF have a cystic component and only 10% are completely solid\(^1\). In tumors with a large cystic component stereotactic drainage or instillation of radioactive and/or chemotherapy agents have been used.

Some patients have been managed by serial aspiration of cyst contents through a subcutaneous Ommaya reservoir connected to a catheter placed inside the cyst, achieving a palliative decompression of the optic nerves and chiasm\(^4\). For many years radioactive agents like Phosphorus-32 and Itrium-90 have been employed achieving high rates of tumor control\(^6\), but they can worsen the endocrino-
logical and visual function in up to a 33 to 58% of the cases respectively. On the other hand, treatment of recurrent CFs pose a particular problem, as the majority of these patients have already received external radiotherapy.

Regarding the instillation of chemotherapeutical agents, some authors have reported good results with the use of intracystic bleomycin. Bleomycin is an antineoplastic antibiotic able to interrupt the synthesis of DNA, which has proved useful in the treatment of scamous cell carcinoma, lymphomas and testicular carcinoma. Intracessional bleomycin has also been used in the treatment of malignant brain tumors, with little morbidity associated to the penetration of the drug into the adjacent cerebral parenchyma.

Recent studies by Broggi et al. about cellular kinetics in CF help to understand the effectiveness of intracystic treatments, as proliferative cells in phase S are mainly localised in the scamous epithelium of the cyst wall. Moreover, other studies have demonstrated that intracystic application of bleomycin in CF diminishes the secretion of cystic fluid and produces the degeneration of tumoral cells.

Treatment of CF with bleomycin was firstly described by Takahashi et al. with excellent results in four patients with cystic tumors. Thereafter, only three other short series of cases and some sporadic case reports on the use of bleomycin in the initial or recurrent treatment of cystic CF have been reported in the literature (Table 1). Results are variable, probably because of the heterogeneity of cases in the series reported; in fact adult and children and primary with recurrent tumors were mixed in the series. What is definitely clear is that the utility of this treatment is poor in solid tumors or in cystic tumors with a large solid component.

There is not an established protocol for the indication and the form of application of intracystic bleomycin. Some authors have used it as the first and the only treatment in cystic CF. Others have used it for the treatment of recurrences or as an adjuvant treatment after an initial partial resection. The majority of authors who have used this treatment administered bleomycin through an Ommaya reservoir connected to a catheter placed in the cyst with the help of stereotactic techniques, although others have inserted it by direct vision through a craniotomy. Some authors performed cystography by injecting contrast into the reservoir to assure that there were no leaks into the subarachnoid space. Then, the majority instilled bleomycin solution after aspiring the same amount of liquid from the cyst. Total doses and time intervals between repeated instillations were variable in the few cases reported in the literature. In our patient we applied a total dose of 45 mg separated into 6 doses given every 48 hours.

There is no agreement in the literature concerning the value of LDH determinations in the liquid of the cyst as a prognostic factor in patients treated with bleomycin, as some authors describe a progressive decrease of enzyme concentration, while others observe little changes or even an increase as occurred in our case. These differences suggest that monitoring LDH levels is not useful for assessing the efficacy of treatment.

Different adverse reactions such as interstitial pneumonia, pulmonary fibrosis, fever, sclerodermic changes in the skin and alopecia have been described after systemic administration of bleomycin in tumors outside the CNS. However, there are no cases of systemic side effects in patients with CNS tumors treated with local bleomycin in CNS.
tumors. However, it has been estimated that the risk of local complications after the administration of intratumoral bleomycin in patients with CF is 10%4. Haisa et al. attributed hypersomnia, thermal deregulation, memory impairment and transient behavioral changes developed by one of their patients to the effect of bleomycin on the hypothalamus19. Other authors have reported cases with transitory fever, ischemic attacks, loss of hearing and blindness4,5,15,17. Recently Savas et al. reported the case of a patient who died several days after the administration of bleomycin into a cystic CF; following neurological deterioration, MR showed diffuse meningeal and diencephalic edema accompanied by a decrease in the size of the cyst19. In our case there were no adverse reactions, neither during treatment nor through a 18 months follow-up.

Adverse reactions seem to be due to the direct effect of bleomycin on the normal brain parenchyma. In some cases this toxic effect has occurred after the impermeability of the cyst was assured on the basis of CT cystography. This is why Harper et al. have suggested that bleomycin may diffuse or react with the adjacent parenchyma through the thin walls of the cyst, or inadvertently escape from orifices of the catheter proximal to the point of insertion into the cyst. For this reason it is strongly recommended to avoid the passage of the catheter through the subarachnoid space or the ventricular system, and taking care for all orifices of the catheter to be placed inside the cyst.

We would like to conclude that until treatment protocols are standardised, intracavitary administration of bleomycin is a valid option as adjuvant therapy for cystic CF, but only in patients with recurrences that are not surgical candidates because of the high risk of complications. The role of bleomycin as a primary treatment for CF remains to be established with more studies.

References


Intratumoural bleomycin as a treatment for recurrent cystic craniopharyngioma. Case report and review of the literature.


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Comentario al trabajo: Intratumoural bleomycin as a treatment for recurrent cystic craniopharyngioma. Case report and review of the literature de J.F. Alén y cols.

Merece unas palabras este trabajo sobre "Recidiva quística de un craneofaringioma", por los autores J.F. Alén y otros.

La cirugía del craneofaringioma viene a ser uno de los paradigmas de la indecisión en el acto operatorio. Si uno se inclina por la exéresis radical pueden producirse secuelas neurológicas muy graves, bien sea en la visión o en el hipotálamo. Si se prefiere un cierto conservadurismo, el riesgo de recidiva es mayor. Por lo tanto, se ha recomendado la radioterapia como complemento a la cirugía, partiendo de la base de que lo dejado escrito en la nota operatoria como extirpación radical puede ser, una vez más, puro espejismo quirúrgico. Es obvio que la radioterapia o radiocirugía no son inocas; por esta razón, deben aplicarse cuando haya evidencia de recurrencia, hoy de no difícil comprobación con la RM.

Como apuntan los autores, las operaciones posteriores son más complejas y laboriosas, con mayor riesgo, por la fibrosis secundarias a la primera operación y al efecto de la radiación. Esta dificultad quirúrgica se acentúa cuando se trata de un proceso quístico, en lugar de un nódulo aislado.

La bleomicina se utilizó como droga antitumoral a principios de la década de los setenta. Tal vez fue la primera frustración en la aplicación de la quimioterapia como tratamiento de los gliomas. A la nula efectividad, había que añadir los efectos secundarios sobre el parénquima pulmonar, cuando se administraba por vía parenteral. Esta frustración ha sido nuestra compañera permanente, ante las expectativas creadas por las nitrosureas, procarbazina, etopósidos, taxoides, derivados del platino, etc, a lo largo del último cuarto de siglo.

Cuando nos encontramos ante la recidiva de un craneofaringioma de carácter quístico, creo que la mejor opción es la elegida por los autores. Con las precauciones adecuadas, descritas en el texto, de cerciorarse de que no hay goteo de la droga fuera del quiste, el riesgo me parece menor que el uso de isótopos, estos últimos de consecuencias adversas menos previsibles. Es posible que con nuevos fármacos, tales como el interferón-alfa-2a, sólo o en combinación con otras drogas, se pueda mejorar el pronóstico. Este último tratamiento tiene la ventaja de administrarse por vía subcutánea. Su efectividad en algunos tumores de estirpe epitelial ha sido el argumento para utilizarlo en los craneofaringiomas, tumores del mismo origen. El tratamiento es largo, no exento de toxicidad y el resultado sólo es el comienzo de una leve esperanza.

En este paciente, con los tratamiento quirúrgicos anteriores se consiguió una supervivencia aceptable. Cabe esperar que con la bleomicina intraquística, el resultado sea aún más eficaz.

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