Spontaneous regression of brain tumors in children: case report and literature review

Regresión espontánea de tumores cerebrales en niños: Reporte de caso y revisión de la literatura

José A. Franco-Jiménez¹, Abrahan A. Tafur-Grandett², Ricardo López-Orozco², Antonio Sosa-Nájera³

¹ Pediatric Neurosurgery Department, Hospital Infantil de México Federico Gómez, National Institute of Health, Mexico City, Mexico.
² Neurosurgery Department, Centro Médico Lic. Adolfo López Mateos, Health Institute of the State of Mexico, Toluca. State of Mexico, Mexico.
³ Department of Neurosurgery, Grupo Neurológico de Alta Especialidad, Hospital Ángeles Morelia. Morelia, Michoacan.

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Resumen

Introducción: Se definen como lesiones ocupantes de espacio que presentan características radiológicas de tumores y que se resuelven espontáneamente durante el seguimiento radiológico. La regresión espontánea de tumores es un fenómeno raro, con una tasa de regresión en tumores malignos de 1/60,000 a 100,000 pacientes. Materiales y Métodos: Femenino de 11 años con polidipsia, poliuria, pérdida de peso de 5 kg, ataxia, cefalea, pérdida de visión y diabetes insípida. TC con tumor dependiente de quiasma que ocupa la cisterna interpenduncular desplazando el hipotálamo ventralmente. Resultados: Se realizó biopsia excisional mediante abordaje pterional y resección microquirúrgica, durante el procedimiento transquirúrgico se encontró engrosamiento del quiasma y nervios ópticos. Se notificó astocitoma pilocítico de grado I de la OMS. En el seguimiento de dos años con resonancia magnética cerebral, observamos una regresión completa del tumor. Discusión: La citorreducción parcial del tumor, biopsia, radioterapia o quimioterapia juegan un papel en el inicio de la apoptosis del tumor. El trauma quirúrgico altera favorablemente la actividad biológica del tumor y el estado inmunológico del huésped. Conclusiones: Los mecanismos de regresión espontánea e involución espontánea del tumor residual después de la cirugía no se conocen. La apoptosis puede ser el denominador común, los posibles mecanismos incluyen factores inmunológicos, genéticos y biológicos.

Palabras clave: Regresión espontánea, astrocitoma pilocítico, tumores cerebrales, apoptosis.

Abstract

Introduction: They are defined as space-occupying lesions that present radiological characteristics of tumors and that resolve spontaneously during radiological follow-up. Spontaneous regression of tumors is a rare phenomenon, with a regression rate in malignant tumors of 1/60,000 to 100,000 patients. Materials and Methods: An 11-year-old female with polydipsia, polyuria, 5 kg weight loss, ataxia, headache, vision loss, and diabetes insipidus. CT with chiasm-dependent tumor occupying the interpenduncular cistern, displacing the hypothalamic ventrally. Results: An excisional biopsy was performed using a pterional approach, microsurgical resection + ultrasonic aspiration, during the trans-surgical procedure thickening of the chiasm and optic nerves was found. WHO Grade I Pilocytic Astrocytoma was reported. In the two-year follow-up with magnetic resonance imaging of the brain, we observed complete tumor regression. Discussion: Partial cytoreduction of the tumor, biopsy, radiotherapy or chemotherapy play a role in the initiation of tumor apoptosis. Surgical trauma favorably
Introduction

They are defined as space-occupying lesions that present radiological characteristics of tumors and that resolve spontaneously during radiological follow-up\(^7\)-\(^16\). Spontaneous regression of tumors is a rare phenomenon, with a regression rate in malignant tumors of 1/60,000 to 100,000 patients\(^31, 32\). There have been sporadic reports of spontaneous regression of intracranial lesions including intracranial metastases from renal cell carcinoma, malignant lymphoma, and glioma associated with neurofibromatosis, pineal germinoma, optic pathway and hypothalamic gliomas associated with neurofibromatosis type 1 (NF1)\(^22, 38\). Until now, the exact triggers that lead to spontaneous tumor regression are unknown\(^31\), however several hypotheses have been proposed regarding the mechanism of spontaneous regression, such as immunological responses, spontaneous apoptosis, hydration effects of drainage of the cerebrospinal fluid and radiation effects using diagnostic X-rays, but these proposed mechanisms remain controversial\(^7, 22, 25\). Parsa et al., suggested that partial debulking of the tumor, biopsy, radiotherapy, or chemotherapy may play a role in initiating tumor apoptosis\(^28\). Others have further described needle biopsy or minor debulking as instigators of regression, citing growth factors and other endogenous reactions as the mechanism\(^4, 17, 29, 33\). Corticosteroid treatment can change the patient's total immune defense mechanism, which is then sufficient to eradicate the intracranial tumor\(^22, 24\). It has also been observed that surgical trauma can favorably alter the biological activity of the tumor or the immunological status of the host\(^1, 27\). Cases of tectal tumor involution after endoscopic third ventriculostomy have been reported; tumor regression has also been experienced after placement of a ventriculoperitoneal shunt (PVS). Because many cases of malignant tumor regression occur after surgery, it is thought that immune function, which is temporarily reduced by surgical invasion and then exacerbated during the recovery period, may be involved in tumor regression\(^22\).

Material and Methods

An 11-year-old female, with a history of Chickenpox at 7 years of age, without complications. History of hospitalization due to a clinical picture compatible with hypopituitarism, for which they were referred to third level care. His condition began with polydipsia, polyuria (10 micturitions per day), weight loss (5 kg), asthenia, adynamia, occasionally ataxic gait (once a month), without triggers or mitigating factors. Subsequently, it presented with throbbing headache predominantly at night in the left parietal region, with frontal irradiation associated with occasional vomiting. Progressive loss of vision predominantly in the right eye. Simple skull CT, where a lesion occupying intracranial space is observed, integrating a diagnosis of probable pituitary adenoma + Diabetes Insipidus. A hormonal profile was performed with the following results: ACTH 22.90, Cortisol 1.92, IDF-1 29.0, total T3 157, total T4 7.18, TSH 2.7, Free T4 0.74, AFP 5.07, \(\beta\) Gonadotropin 1.20. The protocol was completed with CT and she was assessed by Pediatric Neurosurgery, where a chiasm-dependent tumor was reported occupying the entire interpeduncular cistern, displacing the hypothalamus ventrally (Figure 1). Probable Craniopharyngioma/Panhypopituitarism vs probable Pituitary Adenoma is suspected. Evaluation by Ophthalmology, Endocrinology and Oncology is requested. Steroid is started due to tumor ede-
ma. Endocrinology indicated prior to the surgical procedure Levotrioxine 37.5 mcg (0.98 mcg/day) and Hydrocortisone 62.5 mg.

Results

An excisional biopsy was performed using a classic Pterional approach by microsurgical resection + ultrasonic aspiration, during the trans-surgery, significant thickening of the optic chiasm and optic nerves was found. A 0.7x 0.4x0.2 cm sample was sent reporting a WHO Grade I Pilocytic Astrocytoma. He received 18 weeks of chemotherapy with Carboplatin (CBP), presenting visual impairment during the start of the induction scheme with Vincristine 1.5mg/m2 weekly for 4 weeks and CBP 175 mg/m2 weekly for 4 weeks. Subsequently, he presented a good response to chemotherapy with visual recovery and a decrease in tumor volume. During a two-year follow-up with magnetic resonance imaging of the brain, we observed complete tumor regression (Figure 2).

Discussion

Pediatric low-grade gliomas comprise a wide range of central nervous system tumors. These include diffuse astrocytomas, pilocytic astrocytomas, oligodendrogliomas, and others. These tumors share the usual course of slow growth progression; however, progression to high-grade astrocytomas is possible for low-grade astrocytomas, and regression has rarely been reported. Spontaneous regression has not been widely reported in the literature. Several case reports demonstrate that this is a potential course for low-grade gliomas. Of the factors that have been suggested as positive associations for tumor regression, the association with neurofibromatosis has been the most widely reported. Pilocytic astrocytoma (PA) is the most common pediatric brain tumor and the second most common tumor in childhood. PA is usually benign, often follows an indolent course, and is mostly slow-growing. In children, it most often occurs in the cerebellum but can develop throughout the neuraxis. Surgery is the treatment of choice. If total resection is achieved, the prognosis is favorable with a greater than 90% cure rate. However, in many cases tumor location in critical or deep areas (such as the brainstem, optic pathway, or hypothalamus) restricts resection options and alternative management options are required. Patients with only partial resection may regrow or even progress to a more aggressive tumor, but spontaneous tumor regression has also been observed in cases of PA. It is estimated that 14% of all residual cerebellar astrocytomas may regress spontaneously. Due to the possibility of regression and the indolent nature of PA, some authors propose a "wait and see" strategy to avoid potential risks induced by additional therapies. Other authors favor aggressive surgical resection in combination with additional treatment strategies such as radiation and chemotherapy to control tumor growth. No statistically significant independent variables (symptoms, age, sex, histological grade or Ki-67 fraction) were found as predictors of spontaneous regression. Spontaneous involution of other types of low-grade astrocytoma is well recognized in children with NF1, both for optic pathway gliomas and at other intracerebral sites. There are individual case reports of regression of low-grade astrocytoma in children and young adults without NF1. The mechanisms of spontaneous tumor regression and spontaneous involution of residual tumor after surgery are not known. Although programmed cell death or apoptosis may be the common denominator, possible mechanisms include immunological, genetic, and biological factors. Terminal differentiation, in association with inflammation or apoptosis, whereby terminally differentiated cells are no longer capable of cell division and are therefore fatal, is another potential mechanism for spontaneous regression. Immunological mechanisms, including cell-mediated and humoral responses to tumor-associated antigens, can trigger apoptosis, resulting in spontaneous regression. Treatment options range from monitoring, conservative management to biopsy, partial debulking, radical surgical excision, chemotherapy, and radiotherapy. Surgical resection, rather than biopsy, is often recommended for rapid symptom control. Radiation therapy and chemotherapy are often avoided for higher grade tumors or as an adjunct to surgery. A recent review of adjuvant therapy for astrocytomas showed that combination chemotherapy, regardless of regimen, has disappointing results. The most commonly used regimen of carboplatin and vincristine achieves 5% complete responses and 28% complete responses. Partial answers. Chemotherapy is often reserved for children who have failed treatment with surgery and radiation therapy, or who are too young to be treated.
**Table 1. Cases of tumor regression from 1982 to 2020**

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex/ Age</th>
<th>Pathology diagnosis</th>
<th>Presentation</th>
<th>Treatment</th>
<th>Steroid use</th>
<th>Time to regression</th>
<th>Tracing</th>
<th>Regression amount</th>
<th>Regression hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam, et al. 1982</td>
<td>M/50 Y</td>
<td>Hepatocarcinoma</td>
<td>Cirrhosis</td>
<td>Antibiotic therapy for SBP</td>
<td>No</td>
<td>6 Mo</td>
<td>4 Y</td>
<td>Total</td>
<td>HAV infection, immune response</td>
</tr>
<tr>
<td>Venes, et al. 1984</td>
<td>F/18 Y</td>
<td>Pilocytic Astrocytoma</td>
<td>NF1</td>
<td>Biopsy</td>
<td>Yes</td>
<td>18 Mo</td>
<td>26 Mo</td>
<td>Total</td>
<td>Immune response, NF1</td>
</tr>
<tr>
<td>Holmes, et al. 1986</td>
<td>M/32 Y</td>
<td>Testicular Seminoma</td>
<td>Scrotal Growth And Pain</td>
<td>Orchiectomy/ CDDP</td>
<td>No</td>
<td>1 Y</td>
<td>N/R</td>
<td>Total</td>
<td>Surgical trauma</td>
</tr>
<tr>
<td>Sugita, et al. 1988</td>
<td>F/63 Y</td>
<td>Non-Hodgkin’s Lymphoma</td>
<td>Headache, B Symptoms</td>
<td>Tumor resection</td>
<td>Yes</td>
<td>8 Mo</td>
<td>1 Y</td>
<td>Total</td>
<td>Immune response, NF1</td>
</tr>
<tr>
<td>Leisti, et al. 1996</td>
<td>M/8 Y</td>
<td>Pilocytic Astrocytoma</td>
<td>NF1</td>
<td>Biopsy</td>
<td>Yes</td>
<td>12 Y</td>
<td>18 Y</td>
<td>Total</td>
<td>Immune response, NF1</td>
</tr>
<tr>
<td>Fujimaki, et al. 1999</td>
<td>M/39 Y</td>
<td>Germinoma</td>
<td>Headache, seizures, parinaud syndrome</td>
<td>Tumor resection</td>
<td>Yes</td>
<td>8 D</td>
<td>2 Y</td>
<td>Total</td>
<td>Surgical trauma, immune response</td>
</tr>
<tr>
<td>Murai, et al. 2000</td>
<td>M/17 Y</td>
<td>Pineal Gland/Germinoma</td>
<td>Decreased visual acuity, hydrocephaly</td>
<td>VPS</td>
<td>No</td>
<td>1 Y</td>
<td>N/R</td>
<td>Partial</td>
<td>Surgical trauma, VPS</td>
</tr>
<tr>
<td>Di Chirico, et al. 2003</td>
<td>F/16 Y</td>
<td>N/D</td>
<td>Headache</td>
<td>ETV</td>
<td>No</td>
<td>6 Mo</td>
<td>3 Y</td>
<td>Partial</td>
<td>Surgical trauma, VPS</td>
</tr>
<tr>
<td>Masoudi, et al. 2007</td>
<td>M/17 Y</td>
<td>Germinoma</td>
<td>Headache, reduced visual acuity</td>
<td>ETV</td>
<td>Yes</td>
<td>5 D</td>
<td>17 Mo</td>
<td>Partial</td>
<td>Steroid treatment</td>
</tr>
<tr>
<td>F/6 Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Y</td>
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<tr>
<td>M/2 Y</td>
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<td></td>
<td></td>
<td>2 Y</td>
<td></td>
<td></td>
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<tr>
<td>F/4 Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Y</td>
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<tr>
<td>F/6 Mo</td>
<td></td>
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<td></td>
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<td>2 Y</td>
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<tr>
<td>F/3 Y</td>
<td></td>
<td></td>
<td>Pilotocytic astrocytoma</td>
<td>NF1</td>
<td>N/R</td>
<td>N/R</td>
<td>6 Y</td>
<td>N/R</td>
<td>NF1</td>
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<tr>
<td>F/6 Y</td>
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<td></td>
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<td>1 Y</td>
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<tr>
<td>M/3 Y</td>
<td></td>
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<td></td>
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<td></td>
<td>4 Y</td>
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<tr>
<td>F/4 Y</td>
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<td>1 Y</td>
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<tr>
<td>M/2 Y</td>
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<td></td>
<td></td>
<td></td>
<td>8 Y</td>
<td></td>
<td></td>
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<tr>
<td>M/18 Y</td>
<td></td>
<td>Germinoma</td>
<td>Amnesia, blurred vision</td>
<td>None</td>
<td>No</td>
<td>12 D</td>
<td>N/R</td>
<td>Total</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>F/20 Y</td>
<td></td>
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<td>F/21 Y</td>
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<tr>
<td>F/22 Y</td>
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<td>F/23 Y</td>
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</tbody>
</table>

CDDP: Cisplatin; D: Days; ETV: Endoscopic third ventriculostomy; F: Female; HAV: Hepatitis A virus; M: Male; Mo: Months; N/D: No diagnosis; NF1: Neurofibromatosis Type 1; N/R: No report; SBP: Spontaneous bacterial peritonitis; VPS: Ventricule peritoneal shunt; Y: Years.
with radiation. Radiotherapy has had similarly disappointing results, with recent findings suggesting that both lower dose (45 Gy) and higher dose (60 Gy) regimens show no difference in outcomes\(^{13,29}\). We conducted a review of the international literature where we found 23 cases of tumor regression due to different hypotheses and types of tumors, from 1982 to 2020 when we reported our case, which is detailed in Table \(^{1,5,7,8,16,17,20,21,24,29,30,34,38,39,40}\).

**Conclusion**

The mechanisms of spontaneous regression and spontaneous involution of residual tumor after surgery are not known. Apoptosis may be the common denominator, possible mechanisms include immunological, genetic and biological factors. Spontaneous regression has been observed in the literature at a minimum of 7 months and a maximum of 4 years 2 months. In addition to early postoperative examination performed 24-48 hours after surgery, surveillance imaging at 6-month intervals for the first year is recommended. Six-month intervals for the following 2 years would detect those with late tumor progression and annually for a further 2 years would reliably detect those children in whom late spontaneous regression would occur. In conclusion, residual tumor after initial surgical resection following a "watch and wait" policy (surveillance imaging) may regress or progress. Surveillance imaging at 6-month intervals for the first 2 years is recommended for all children with known residual disease. Scanning should be continued at 3, 4, and 5 years after the initial surgery, and then every 2 years if residual tumor is still present at 5 years after surgery. This regimen would detect not only children with progressive or recurrent disease, but also those with spontaneous regression, a phenomenon that may occur later than disease progression.

**References**

23. Ogiwara H, Bowman RM, Tomita T. Long-term follow-up


