Radiation-associated Pituitary Sarcoma: Case Report and Review of Literature

Sarcoma Hipofisário Radio-Associado: Relato de Caso e Revisão da Literatura

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ABSTRACT

Background: Radiation therapy is commonly used as primary or adjuvant treatment for pituitary adenomas. Frequent side effects of this modality include hypopituitarism, visual disturbances, short-term memory loss and secondary tumors, sarcomas being among the rarest of the sellar region, with only 55 reported cases to date. Clinical Presentation: A 57-year old man with hypopituitarism and a 20-year history of a non-functioning pituitary macroadenoma subtotally resected four times and undergoing whole brain radiotherapy and bromocriptine, who developed acute visual deterioration due to compression of the optic chiasm by rapid growth of the residual tumor. An endoscopic transplanum approach was performed achieving gross total resection. Histopathological examination was consistent with an undifferentiated low-grade pituitary sarcoma. The patient’s vision improved after surgery, but healthcare-associated complications compromised his clinical outcome, succumbing to a pulmonary embolism a month after surgery. Conclusion: Radiation-induced pituitary sarcoma is a very rare complication of radiotherapy. There is no distinctive feature on imaging that can predict its occurrence. Prognosis is grim, without effective management and a mean survival of 6.5 months after diagnosis.

Key words: Pituitary neoplasms, Radiation-induced neoplasms, Sarcoma.

RESUMO

Introdução: A radioterapia normalmente é utilizada como tratamento primário ou complementar para adenomas pituitários. Os efeitos colaterais mais frequentes incluem hipopituitarismo, distúrbios visuais, perda de memória recente e tumores secundários. Sarcomas estão entre as neoplasias mais raras na região selar com somente 55 casos relatados. Caso Clínico: Paciente masculino de 57 anos de idade com hipopituitarismo e uma história de 20 anos de macroadenoma hipofisário não-funcionante, com quatro ressecções subtotais e radioterapia cerebral total e uso de bromocriptina. Desenvolveu deterioração visual aguda devido à compressão do quiasma óptico por rápido crescimento do tumor residual. Foi realizado um acesso endoscópico transplano obtendo ressecção total. O exame histopatológico foi consistente com sarcoma pituitário de baixo grau. A visão do paciente melhorou após a cirurgia, embora complicações associadas tenham comprometido o resultado clínico, resultando em óbito por embolia pulmonar um mês após o procedimento. Conclusão: O sarcoma pituitário radio-induzido é uma rara complicaçao da radioterapia. Não há característica peculiar na imagem que possa predizer sua ocorrência. O prognóstico é ruim, sem um tratamento eficaz, com sobrevida média de 6,5 meses após diagnóstico.

Palavras-chave: Neoplasias pituitárias, Neoplasias radio-induzidas, Sarcoma.

BACKGROUND

Radiation therapy is a well-established option for the management of pituitary adenomas. Used as primary or adjuvant treatment, it has proven effective in tumor control, but treatment-related toxicity, commonly grouped as radiation-induced brain disorders (RIBD) has limited its use. Hypopituitarism, stroke and visual deterioration are among the most common long-term side effects of radiotherapy, with a widely varying incidence according to the follow-up period2,8. Secondary central nervous system (CNS) tumors are rarer entities among RIBD, being meningiomas, nerve-sheath tumors, pituitary adenomas, and gliomas the most
commonly encountered. The risk of developing radiation-induced CNS tumors has been associated with radiation at early age and a high cumulative radiation dosage, with greater exposures generally associated with shorter latency period and higher risk of malignancy\cite{7,14}. For pituitary adenomas treated with radiotherapy, long-term retrospective analyses estimate a 20-year risk of any second intracranial tumor to be around 1.9 to 2.4\%\cite{8,12}, with earlier studies giving higher\cite{8,19}, or even lower incidences\cite{4,9}; discrepancies mainly attributed to follow-up periods, radiation dose and the use of imaging techniques during long-term monitoring\cite{12}. To date, there is no estimate incidence of radiation-induced CNS sarcomas.

Secondary pituitary sarcoma is a rare complication of radiation therapy for pituitary adenomas. Initial reports quickly established an association with low-dose multiple radiotherapy cycles and cumulative doses over 30Gy\cite{10}. Since 1959, only 55 cases of sellar sarcomas after radiotherapy for benign pituitary tumors have been reported\cite{2,17,18,20}.

Amendola et al. revised Cahan’s criteria for radiation-induced sarcomas and stated that the new tumor must differ histologically from the original lesion that was treated, must arise within the irradiation field over a sufficient latency period -usually years to decades-, and the diagnosis must be proven histologically\cite{1,5}. The cellular origin of a pituitary sarcoma cannot be certainly determined, however, the interlacing of sarcomatous and adenomatous components implies that the sarcomatous component is derived from the pre-existing pituitary adenoma\cite{15}

\section*{Clinical Presentation}

In 1990, a 35-year-old male was referred to the Ophthalmology Clinic of the Regional Clinical Hospital of Concepción, Chile, due to progressive peripheral vision loss over a 2-year time period. After multidisciplinary evaluation, an isolated bitemporal hemianopia was found. Head computed tomography (CT) evidenced a sellar mass with significant suprasellar extension. Endocrinological evaluation showed no pituitary hormone disfunction. Thus, the patient underwent transcranial adenomectomy via right frontal craniotomy, which evidenced a greyish, friable tumor surrounding both optic nerves. Subtotal resection was achieved, with histopathological examination showing a sinusoidal-type pituitary adenoma.

Two months later, the patient underwent whole-brain cobalt-60 radiation therapy centered on the pituitary region. A total dose of 50.4 Gy was delivered over a month. Short-term follow-up evidenced mild improvement on Goldmann visual field test and the appearance of a persistent holocranial headache. No postoperative imaging was performed at that time.

Three years later, the patient was admitted following progressive visual field deterioration. Head CT showed the residual tumor extending up to the floor of the third ventricle. In April 1993, a new transcranial approach was performed, with wide decompression of the optic chiasm, which was infiltrated by a fibrous tumor, again, only partially resected. Biopsy report this time informed a solid-type pituitary adenoma. At follow-up, his visual field deficit stalled, but his headache persisted, therefore, the neuro-oncologic committee proposed beginning bromocriptine.

The patient’s neurological condition stabilized and bromocriptine was continued for seven years, on which he developed secondary adrenal insufficiency. In April 2001, a brain magnetic resonance imaging (MRI) showed the residual tumor occupying the entire sella turcica and suprasellar cistern, so a microscopic sublabial transphenoidal surgery was performed, with appropriate resection of the tumor along the sphenoidellar axis. The closure required a fat graft to cover a significant osteo-meningeal breach, developing a transient cerebrospinal fluid (CSF) fistula, nonetheless. Pathology report informed a diffuse-type pituitary adenoma with focal cicatricial fibrosis. After surgery, bromocriptine was discontinued. Follow-up at 6 months noted the occurrence of hypothyroidism and hypogonadotropic hypogonadism, beginning replacement therapy accordingly. MRI showed a calcified intrasellar residue with right cavernous sinus extension.

Clinical evolution remained uneventful until 2011, when routine ophthalmological evaluation evidenced right-eye peripapillary atrophy and right temporosuperior quadrant anopia. An MRI was obtained, showing significant growth of the residual tumor with suprasellar extension. Therefore, an endoscopic endonasal resection was performed, with partial excresis, sufficient to decompress the optic nerve, but with a right cavernous sinus and suprasellar remnant. The tumor was fibrous and very adherent to the surrounding structures, which limited the surgical effort for complete removal. Pathology report informed...
fibrous tissue extensively infiltrated by pituitary adenoma. Immunohistochemistry showed a Ki-67 labelling index of 5% and focal positivity for prolactin, Thyroid-stimulating hormone (TSH) and Adrenocorticotropic hormone (ACTH) staining. Immediately after surgery, the patient developed permanent diabetes insipidus.

Frequent outpatient follow-up was maintained, which led to early recognition of a progressive left optic atrophy, with a new MRI that showed a focal “budding” of the tumor dome that was not present on the previous MRI, 6 months earlier (Figure 1A, 1B, 1C). In March 2013, the patient underwent an extended endoscopic transphenoidal-transplanum approach. A fibrous, highly vascularized tumor was encountered, with firm adhesion to the surrounding structures, namely both cavernous sinuses. Gross total resection was achieved, beginning by internal debulking of the tumor with an ultrasonic aspirator, followed by piecemeal resection of the capsule using the ultrasonic aspirator as cutting device. After resection, endoscopic examination of the cavity showed a free suprasellar cistern, third ventricle, optic chiasm and both internal carotid arteries. Reconstruction of the surgical defect was achieved by inlay fat and fascia lata graft followed by fibrin glue. A nasoseptal flap was not feasible as there was no appropriate mucosa due to previous surgeries. No nasal plugs were placed (Figure 2).

In the immediate postoperative period the patient developed healthcare-associated pneumonia, which extended his stay at the intensive care unit, finally succumbing to a massive pulmonary embolism a month after surgery.

Histopathological examination of the pituitary samples showed a low-grade hypercellular tumor, with spindle and round cells and low-to-moderate cytologic atypia, without recognizable pattern, intertwined with a pituitary adenoma with focal ACTH staining. Immunohistochemistry was positive for Vimentin, with a Ki-67 labelling index of 10% in the sarcomatous area (Figure 3A, 3B, 3C). Synaptophysin, Epithelial membrane antigen (EMA), Glial Fibrillary acidic protein (GFAP) and S100 stainings were negative. These findings were consistent with a low-grade pituitary sarcoma, diagnosis that was subsequently confirmed at the University of Texas MD Anderson Cancer Center.
Radiation-induced CNS neoplasms are uncommon complications of radiotherapy with a strong dose-response relationship. To the best of our knowledge, there is no imaging technique that can distinctly differentiate a sarcomatous change from a recurrence of the adenoma, but its occurrence may be suspected in a pituitary recurrence after five or more years of radiation therapy, or a non-functioning recurrence of a previously-functioning adenoma after radiotherapy. Late-onset diabetes insipidus may provide an important suspicion clue, as true recurrence of an adenoma would rarely invade the posterior pituitary. MRI may show characteristic, but non-specific features of other high-grade lesions, such as contrast enhancement, invasion of surrounding structures and increased metabolic activity within the lesion on spectroscopy.

Radiation-induced pituitary sarcomas are highly aggressive and with exceptionally poor prognosis, in spite of the lack of metastases (except for 1 case of meningiosis sarcomatosa), with death occurring about 6.5 months after diagnosis, which greatly differ from primary pituitary sarcomas, being even rarer and with a more favorable overall survival.

Given its rarity, there is no standardized management for this kind of lesion. Surgical resection has been proven ineffective, mainly due to the tumor adhesion to surrounding structures, making total gross resection not always feasible. Radiation is precluded due to previous use, and chemotherapy has not shown to be beneficial.

This case presents a rather unusual opportunity to evaluate the history of an invasive pituitary tumor. Subtotal resections limited by the surgical technique available at those times, allowed characterization of the tumor histopathological features and its change over time, with appearance of sarcoma just two years after a biopsy-proven adenoma, and a focal growth of the tumor residue evidenced by two MRI, six months apart.

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11. Nishio S, Morioka T, Inamura T, Takeshita I, Fukui M, Sasaki M, et al. Radiation-induced brain tumours: potential late onset diabetes insipidus may provide an important suspicion clue, as true recurrence of an adenoma would rarely invade the posterior pituitary. MRI may show characteristic, but non-specific features of other high-grade lesions, such as contrast enhancement, invasion of surrounding structures and increased metabolic activity within the lesion on spectroscopy.

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