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Diagnostic radiation-induced regression of a metastatic primary intracranial germinoma: a case report

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Abstract

Pineal region germinomas are sensitive to radiotherapy. Standard neurosurgical management involves obtaining a tissue biopsy and to relieve the often accompanying obstructive hydrocephalus. We present a patient with a suspected hyper-radiosensitive metastatic primary intracranial germinoma where computed tomography scanning resulted in tumor regression before radiotherapy could be administered.

Keywords

germinoma; computed tomography; radiotherapy; tumor regression

Introduction

Primary intracranial germ cell tumors (ICGCTs) are remarkably radiosensitive and potentially curable when standard radiotherapy (RT) is offered.¹ They are frequently located at the pineal region and only eight histologically proven tumors, all of them germinomas, have been described to exhibit the unique phenomenon of spontaneous regression before RT is initiated.^{2–9} The mechanism is unclear and is believed to be spontaneous, but others have attributed the cause to incidental diagnostic x-ray exposure.^{8,9} We present a case of a young Chinese male with a primary pineal region germinoma with multiple intracranial metastases that underwent regression before definitive radiotherapy was prescribed. We hypothesize

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that ionizing radiation from computed tomography (CT) scanning might have been the cause.

Case report

A 21-year-old Chinese man experienced dizziness, repeated vomiting and polyuria for two months. Physical examination showed papilloedema, but no evidence of Parinaud's syndrome. A non-contrast enhanced CT brain scan revealed a pineal region lesion with calcification causing obstructive hydrocephalus. Subsequent magnetic resonance imaging (MRI) showed multiple heterogeneous gadolinium contrast-enhancing intraventricular tumors with the largest at the pineal region (height $\times$ width $\times$ length: $2.6 \times 3.1 \times 3.3$ cm; volume: 8.9cc), anterior third ventricular floor ($2.0 \times 2.0 \times 1.9$ cm; 2.5cc), right foramen of Monro ($0.9 \times 0.9 \times 1.0$ cm; 0.4cc) and roof of the fourth ventricle ($1.2 \times 1.2 \times 0.9$ cm; 0.6cc) (Figure 1(a)). Serum tumor marker levels for carcinoembryonic antigen (CEA), beta-human chorionic gonadotropin (beta-hCG), and alpha fetoprotein (AFP) were all within the normal range. Panhypopituitarism was diagnosed therefore hydro-cortisone (20mg twice daily), thyroxine and desmopressin were prescribed.

Endoscopic biopsy of the suprasellar tumour and third ventriculostomy for the relief of the obstructive hydrocephalus was performed (Figure 1(b,c)). CEA, beta-HCG, AFP and tumor cells were not detected in the cerebrospinal fluid. Two CT brain scans were performed on postoperative day one and day five to monitor ventricular size. However, the tumor tissue biopsied from the suprasellar lesion revealed numerous lymphocytic infiltrates without discernible tumor cells (Figure 1(d)). A histological diagnosis could not be established therefore a second endoscopic biopsy procedure of the pineal lesion was performed 12 days later. Intraoperatively it was noted that the suprasellar, septal and pineal tumors had significantly regressed. Postoperatively, a fourth and final CT scan was performed to rule out intraventricular hemorrhage culminating in a total brain radiation exposure of 8mSv (or 0.8cGy). A second MRI performed three weeks after the first, revealed considerable regression of all the tumours. Volumetric analysis of the contrast-enhancing lesions showed a 61% reduction in tumor volume for the pineal region lesion ($1.6 \times 2.4 \times 1.8$ cm; 3.5 cc), 77% for the third ventricular lesion ($1.6 \times 1.4 \times 0.9$ cm; 0.7cc), 80% for the foramen of Monro lesion ($0.5 \times 0.8 \times 0.6$ cm; 0.1cc) and 67% for the fourth ventricular lesion ($0.9 \times 0.9 \times 0.6$ cm; 0.2cc) (Figure 1(e–g)). Combined, there was a mean 71% reduction in intracranial tumor volume. Histopathological examination of the second biopsy specimen revealed large neoplastic cells admixed within a lymphoid rich background (Figure 1(h)). Immunohistochemistry revealed SALL4, OCT3/4 and PLAP positivity confirming the diagnosis of germinoma (Figure 2). A subsequent one-month spinal MRI revealed no evidence of drop metastasis. In spite of the clear indications for standard cranio-spinal radiotherapy, the patient wanted to defer such treatment and a third MRI performed three months after initial presentation showed an increase in the size of the pineal and suprasellar region tumors (Figure 1(i)). A time-line of the scans with regard to the operative procedures are exhibited in Figure 1(j).

Discussion

In general, spontaneous regression of malignant tumors is rare and is estimated to occur in 1 in 60 000 to 100 000 patients.¹⁰ With regard to primary ICGCTs, there have been sporadic reports describing germinomas exhibiting this phenomenon before the initiation of standard treatment.^{2–4,8} It is interesting to note that spontaneous regression has been observed more commonly in the Asian population (Table 1). This may be due to the higher incidence of primary ICGCTs in children and young adults of Asian descent that constitute 14% of all pediatric central nervous system (CNS) tumors in Japan and Taiwan compared to 5% in the United States.^{11–13} Thirteen cases of “spontaneous” pineal tumor regression have been reported in the literature with only nine (69%) having a histologically confirmed diagnosis.¹⁴ Within this group, the majority of lesions were germinomas comprising 67% of cases (n = 6).¹⁴

Although the exact mechanisms culminating in intracranial germinoma regression are unclear, three hypotheses may have accounted for the synchronous multifocal reduction in tumor volume observed in our patient. They include ionizing radiation by diagnostic x-ray exposure, perioperative steroid therapy and surgical trauma.

Our case supports the theory that inadvertent x-ray exposure by diagnostic CT brain scanning was the likely cause for tumor regression. Intracranial pure germinomas are highly radiosensitive and carry an excellent prognosis with fractionated RT at a standard dose of 40–45 Gy with ten-year survival rates of 90–100%.¹ As a reflection of their sensitivity, reports of tumor shrinkage after a single 11 Gy dose of radiotherapy or after 10 Gy, administered over five fractions, have been reported.^{15,16} In rarer instances such as ours, a subgroup of germinomas may even be hypersensitive to diagnostic radiation and two other reports support this postulation. Ono et al described a pineal germinoma patient that underwent five CT scans and a single diagnostic catheter angiogram with considerable tumor regression observed within two weeks.⁸ Another patient with multiple metastatic intraventricular germinomas had synchronous regression eight days after a single CT scan and catheter angiogram.⁹ All three patients, including the present case, did not receive glucocorticoid medication. Our experience is unique in that we were able to not only intraoperatively verify intraventricular tumor shrinkage during the second endoscopic procedure and obtain tissue for histological comparison, but we also observed regression with subsequent rebound growth after no further CT scanning.

Preoperative corticosteroids, due to their lymphocytotoxic properties, have also been proposed to be a causative factor for germinoma regression.⁷ This theory is largely founded on their remarkable effect in the treatment of lymphoreticular malignancies such as leukemia and in primary CNS lymphomas.^{17,18} A striking feature of intracranial germinomas is the considerable presence of tumor-infiltrating lymphocytes (TIL). The number of TILs could be so numerous as to obscure the underlying tumor cells and, as exhibited by our case’s first biopsy specimen, can pose diagnostic challenges.¹⁹ The prescription of potent glucocorticoids can theoretically reduce tumor mass, but since only maintenance hydrocortisone was administered for our patient’s hypopituitary hypocortisolism we believe this was unlikely to be the underlying mechanism.^{6,7,20} Furthermore, a review of 153

patients with histologically proven germ cell tumors that were prescribed at least 280mg of postoperative prednisolone did not detect a single case of tumor shrinkage before definitive onco-logic therapy.²¹

In contrast to steroid-induced immune suppression others have suggested that surgical trauma per se could precipitate an inflammatory anti-tumor response.^{3,4,7,22} Simultaneous pineal germinoma regression was described after the resection of a cerebellar lesion, and in another patient after the simple placement of a ventriculoperitoneal shunt.^{3,4} Murai et al postulated that surgery transiently suppressed the immune host response and the following rebound reaction during the postoperative recovery phase led to germinoma regression.⁴ The synchronous regression of all tumor deposits supports this theory of a systemic immune response, but it could not explain the pronounced reduction of TILs in our patient's second tumor specimen. One could argue that pre-existing differences in lymphocytic infiltration from the metastatic lesion (first biopsy site) and the pineal parent tumor (second biopsy site) may have been present, but the relatively paucity of such cells from the larger primary lesion, wherein according to this theory significantly more was expected, still could not be resolved. The role of TILs within germinomas, the majority being T-cells, remains enigmatic. In-vitro studies observed that circulating cytotoxic and helper T-cells inhibited germinoma growth with TILs originally believed to serve as a form of adaptive cancer immunosurveillance.²³ But recent immunophenotyping and mRNA expression analyses have elucidated the dual role of TILs in both suppressing and promoting germinoma cell growth.¹⁹ Therefore given the current lack of understanding of the complex interplay between immune and tumor cells drawing definitive conclusions on the hypothesis of immune-mediated tumor regression may be premature.

In addition to the aforementioned hypotheses, Schipmann et al proposed three other mechanisms for tumor regression including: 1. pineal apoplexy; 2. CSF diversion-induced intracranial pressure normalization causing the displacement of intratumoral cyst fluid into the ventricular system; and 3. immune-mediated reactions triggered by CNS infection.¹⁴ Our report does not support these hypotheses since the patient had simultaneous regression of all lesions; they were predominantly solid without any cystic components and bacterial ventriculitis did not occur.

The only common denominator for all intracranial germinoma cases that underwent "spontaneous" regression in the literature was diagnostic x-ray radiation exposure with shrinkage occurring as early as five days (Table 1). Therefore one cannot rule out this possibility as the main precipitating cause. Regardless of the mechanism of this peculiar phenomenon, intracranial germinomas are increasingly being identified as being "ghost tumors".²⁴ The clinician should be cognizant of the potential confounding effects of diagnostic irradiation before the establishment of a histological diagnosis. We recommend that one should limit the number of CT brain scans for patients with suspected intracranial germinomas. For pineal lesions causing obstructive hydrocephalus requiring CSF diversion, diligent postoperative clinical neurological assessment and ICP monitoring could substitute the need for frequent scanning.

References

1. Kim JY, Park J. Understanding the treatment strategies of intracranial germ cell tumors: focusing on radiotherapy. *J Korean Neurosurg Soc.* 2015;57(5):315–22. [PubMed: 26113957]
2. Ide M, Jimbo M, Yamamoto M, Hagiwara S, Aiba M, Kubo O. Spontaneous regression of primary intracranial germinoma. A case report. *Cancer.* 1997;79(3):558–63. [PubMed: 9028368]
3. Fujimaki T, Mishima K, Asai A, Suzuki I, Kirino T. Spontaneous regression of a residual pineal tumor after resection of a cerebellar vermian germinoma. *J Neurooncol.* 1999 Jan;41(1):65–70. [PubMed: 10222424]
4. Murai Y, Kobayashi S, Mizunari T, Ohaki Y, Adachi K, Teramoto A. Spontaneous regression of a germinoma in the pineal body after placement of a ventriculoperitoneal shunt. *J Neurosurg.* 2000;93(5):884–6. [PubMed: 11059673]
5. Sato A, Sakurada K, Kuge A, Ito M, Akasaka M, Kayama T. [Spontaneous regression of primary intracranial germinoma: a case report]. *No Shinkei Geka.* 2009;37(3):277–82. [PubMed: 19306648]
6. Masoudi A, Amini E, Wolff JE, Fuller GN, Ketonen L, Mahajan A. Shrinkage of germinoma by dexamethasone only. *Pediatr Blood Cancer.* 2008;50(5):1079. [PubMed: 18000859]
7. Si SJ, Khatua S, Dhall G, Nelson MD, Gonzalez-Gomez I, Finlay JL. Regression of primary central nervous system germinoma after dexamethasone administration: a case report. *Pediatr Hematol Oncol.* 2010; 27(3):237–43. [PubMed: 20367268]
8. Ono H, Shin M, Takai K, Oya S, Mukasa A, Saito N. Spontaneous regression of germinoma in the pineal region before endoscopic surgery: a pitfall of modern strategy for pineal germ cell tumors. *J Neurooncol.* 2011;103(3):755–8. [PubMed: 20949306]
9. Yoneoka Y, Tsumanuma I, Jinguji S, Natsumeda M, Fujii Y. Synchronized multiple regression of diagnostic radiation-induced rather than spontaneous: disseminated primary intracranial germinoma in a woman: a case report. *J Med Case Rep.* 2011;5:39. [PubMed: 21272331]
10. Cole WH. Efforts to explain spontaneous regression of cancer. *J Surg Oncol.* 1981;17(3):201–9. [PubMed: 6166811]
11. Wong TT, Ho DM, Chang KP, et al. Primary pediatric brain tumors: statistics of Taipei VGH, Taiwan (1975–2004). *Cancer.* 2005;104(10): 2156–67. [PubMed: 16220552]
12. Makino K, Nakamura H, Yano S, Kuratsu J, Kumamoto Brain Tumor G. Population-based epidemiological study of primary intracranial tumors in childhood. *Childs Nerv Syst.* 2010;26(8):1029–34. [PubMed: 20349186]
13. Villano JL, Propp JM, Porter KR, et al. Malignant pineal germ-cell tumors: an analysis of cases from three tumor registries. *Neuro Oncol.* 2008;10(2):121–30. [PubMed: 18287340]
14. Schipmann S, Keurhorst D, Kochling M, et al. Regression of pineal lesions: spontaneous or iatrogenic? A case report and systematic literature review. *World Neurosurg.* 2017;108:939–47e1. [PubMed: 28844909]
15. Aydin F, Ghatak NR, Radie-Keane K, Kinard J, Land SD. The short-term effect of low-dose radiation on intracranial germinoma. A pathologic study. *Cancer.* 1992;69(9):2322–6. [PubMed: 1562979]
16. Casentini L, Colombo F, Pozza F, Benedetti A. Combined radiosurgery and external radiotherapy of intracranial germinomas. *Surg Neurol.* 1990 Aug;34(2):79–86. [PubMed: 2195685]
17. Frei E 3rd, Karon M, Levin RH, et al. The effectiveness of combinations of antileukemic agents in inducing and maintaining remission in children with acute leukemia. *Blood.* 1965;26(5):642–56. [PubMed: 5321112]
18. Takekawa H, Hozumi A, Hirata K, Yamazaki K. A spontaneously vanishing primary cerebral lymphoma “ghost tumour”. *J Neurol Neurosurg Psychiatry.* 2008;79(10):1159. [PubMed: 18796594]
19. Zapka P, Dorner E, Dreschmann V, et al. Type, frequency, and spatial distribution of immune cell infiltrates in CNS Germinomas: evidence for inflammatory and immunosuppressive mechanisms. *J Neuropathol Exp Neurol.* 2018;77(2):119–27. [PubMed: 29237087]
20. Mascacchi M, Roncaroli F, Salvi F, Frank G. Transient regression of an intracranial germ cell tumour after intravenous steroid administration: a case report. *J Neurol Neurosurg Psychiatry.* 1998;64(5):670–2. [PubMed: 9598688]

21. Matsutani M, Sano K, Takakura K, et al. Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. *J Neurosurg.* 1997;86(3):446–55. [PubMed: 9046301]
22. Yakolev A, Boucher K, DiSario J. Modeling insight into spontaneous regression of tumors. *Math Sbiosci.* 1999;155:45–60.
23. Sawamura Y, Hamou MF, Kuppner MC, de Tribolet N. Immunohistochemical and in vitro functional analysis of pineal-germinoma infiltrating lymphocytes: report of a case. *Neurosurgery.* 1989; 25(3):454–7; discussion 7–8. [PubMed: 2671789]
24. Frassanito P, Tamburrini G, Massimi L, Caldarelli M, Di Rocco C. Ghost tumors of the central nervous system: definition, clinical implications, and proposal of classification. *World Neurosurg.* 2015;84(3): 663–70. [PubMed: 25862114]

Figure 1.

MRI scan revealing a pineal region contrast-enhancing tumor with multifocal spread to the anterior third ventricle (white arrow), right Foramen of Monro (FoM, white arrowhead) and the roof of the fourth ventricle (a; sagittal, T1-weighted sequence). Neuroendoscopic views showing the tumor at the right FoM (b; grey arrowhead) and floor of the third ventricle obscuring the infundibular recess (c; grey arrow). Histological examination of the third ventricular tumor biopsy specimen revealed diffuse lymphocytic infiltration with few intermingling atypical cells harboring pleomorphic hyperchromatic nuclei (d; hematoxylin and eosin stain). Two-week MRI depicting a significant reduction in volume of all lesions (e; sagittal T1-weighted contrast-enhanced sequence). Repeat neuroendoscopy showed corroborative findings with tumor regression at the FoM (f) and third ventricle (g). A subsequent biopsy of the pineal region tumor showed significantly fewer, but still abundant presence of lymphocytes. Large neoplastic cells with prominent nuclei were noted (h). More than two months later, without further CT scanning or formal radiotherapy, there was a rebound increase in the size of all the lesions (i, sagittal T1-weighted contrast-enhanced sequence). Sequence of events demonstrating the temporal relationship between CT scanning and tumor regression (j).

Figure 2.
The tumor cells did not display CD117 reactivity (a), but were positive for OCT3/4 (b), SALL4 (c) and PLAP (d) immunohistochemical markers confirming the diagnosis of germinoma.

Table 1.
Histologically confirmed cases of intracranial Germinoma that underwent spontaneous regression

Author/Year	Age/Sex/ Race	Symptoms	Single/ multiple	Lesion location	Size before regression (max □)	Operation before regression	Glucocorticoid medication before regression detected (Y/N)	Diagnostic irradiation before regression detected	Degree of regression	Period from first diagnostic irradiation to regression detection
Ide <i>et al</i> / 1997	21/M/ Japanese	Headache and cranial diabetes insipidus	Single	Suprasellar	> 20 mm	VP shunt	N	1 CT	Partial	6 days
Fujimaki <i>et al</i> / 1999	39/M/ Japanese	Headache, Parinaud syndrome, seizures and stupor	Multiple	Pineal Cerebellar	> 20 mm N.A.	Craniotomy for Y excision of the 4th ventricular tumor		1 SXR 1 DSA	Partial	23 days
Murai <i>et al</i> / 2000	17/M/ Japanese	Headache and Parinaud syndrome	Single	Pineal	30 mm	VP shunt	N	7CTs	Partial	69 days
Sato <i>et al</i> / 2009	13/M/ Japanese	Headache and cranial diabetes insipidus	Multiple	Pineal Suprasellar	20 mm 13mm	None	N	1 CT	Partial	13 days
Masoudi <i>et al</i> / 2010	17/M/ African- American	Headache and decrease in VA	Single	Pineal	38mm	ETV Biopsy	Y	2 CTs	Partial	5 days
Si <i>et al</i> / 2010	18/M/ Hispanic	Headache with Parinaud syndrome, diplopia and memory problems	Multiple	Pineal Suprasellar	N.A.	Craniotomy for pineal tumor biopsy	Y	1 CT	Partial	N.A.
Ono <i>et al</i> / 2011	15/IW/ Japanese	Headache, diplopia with decrease in VA	Single	Pineal	60 mm	ETV Biopsy	N	4 CTs 1 DSA	Partial	14 days
Yoneoka <i>et al</i> / 2011	43/F/ Japanese	Memory problems with decreased VA	Multiple	Pineal 3rd ventricle Lateral ventricle 4th ventricle	32 mm 10mm 6 mm 9 mm	None	N	1 CT 1 DSA	Partial	12 days
Present case/ 2018	21/M/ Chinese	Headache and cranial diabetes insipidus	Multiple	Pineal FoM 3rd ventricle 4th ventricle	33 mm 10mm 20 mm 12mm	ETV Biopsy	N	4 CTs	Partial	16 days

N.B. □: diameter; VP: ventriculoperitoneal; N.A.: not available; CT: computed tomography; SXR: skull x-ray; DSA: digital subtraction angiography; ETV: endoscopic third ventriculostomy