

Intracranial multiple midline germinomas: is histological verification crucial for therapy?

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ABSTRACT

In this report we present two patients with intracranial multiple midline tumours in the suprasellar region and pineal gland. We postulate that in a patient with multiple midline tumours and normal values of the tumour markers human chorionic gonadotropin and α -fetoprotein in serum and cerebrospinal fluid, the only possible diagnosis is a germinoma. In such a situation no histological confirmation is required to start low-dose radiotherapy.

KEYWORDS

Diabetes insipidus, germ cell tumour, germinoma, radiotherapy

INTRODUCTION

Germinomas belong to the class of germ cell tumours that also comprises embryonal cell carcinoma, yolk sac tumour, teratoma (mature and immature) and choriocarcinoma.¹ Extragonadal germ cell tumours typically arise in midline locations. The most common sites of origin in adults are the anterior mediastinum, retroperitoneum and the pineal and suprasellar regions of the brain.

Primary intracranial germ cell tumours are rare, accounting for 2% of all primary intracranial brain tumours in adolescents and young adults, with a higher incidence in Japan.² Approximately two-thirds of intracranial germ cell tumours are germinomas. Similar to their histological counterparts testicular seminoma and ovarian dysgerminoma, germinomas are extremely radiosensitive and have an excellent overall survival rate of 91 to 97%.¹

Germ cell tumours may present with hypopituitarism in combination with neurological symptoms due to

synchronous lesions in the pineal and suprasellar regions. These multiple midline lesions are almost exclusively germinomas.³ Because of the excellent prognosis of germinomas after radiotherapy, some feel that radiotherapy can be started without tissue diagnosis in the case of multiple tumours located in the midline of the brain, in the pineal and suprasellar regions.⁴ Whether or not this approach is justified will be discussed on the basis of our experience with two patients with intracranial multiple midline tumours.

CASE REPORTS

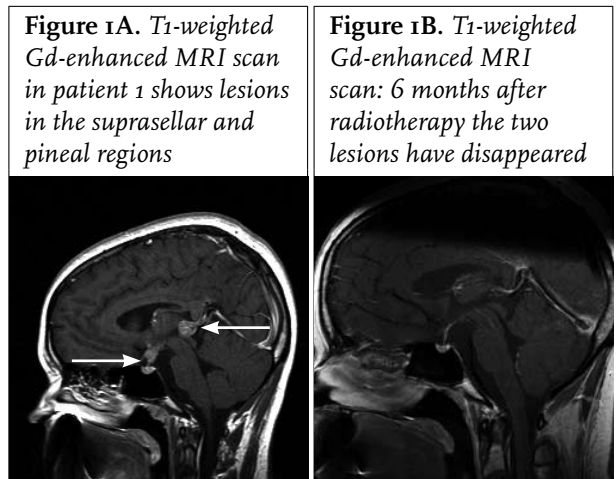
Case 1

A 16-year-old young lady presented with a five-month history of bilateral visual impairment followed by progressive headaches without nausea or vomiting. She did not complain of any other neurological symptoms. Visual acuity was 0.1 on the left and 0.8 on the right. Funduscopic examination revealed bilateral atrophy of the optic nerve. Additional neurological and general physical examination revealed no abnormalities. The differential diagnosis included mononeuritis optica and benign intracranial hypertension. Investigation of the cerebrospinal fluid (CSF) was unremarkable. Methylprednisolone was started at 1000 mg/daily on three consecutive days without effect. Because of positive *Borrelia* serology, chronic Lyme disease was suspected and she was treated with ceftriaxone intravenously, again with no effect. A few months later she developed further visual impairment. At that time, she complained of polyuria and polydipsia. Diabetes insipidus was confirmed by a thirst test. Further endocrinological testing showed panhypopituitarism. A magnetic resonance imaging (MRI) scan showed a thickened pituitary stalk and a mass in the pineal gland (*figure 1A*). Hydrocephalus

was not present. CSF cytology showed lymphocytosis, monocytosis and tumour cells with immunohistochemical expression of cytokeratin (MNF 116). No α -fetoprotein or human chorionic gonadotropin (hCG) could be detected in the CSF.

A stereotactic biopsy of the pineal region was performed. Histological examination of the tissue was compatible with germinoma.

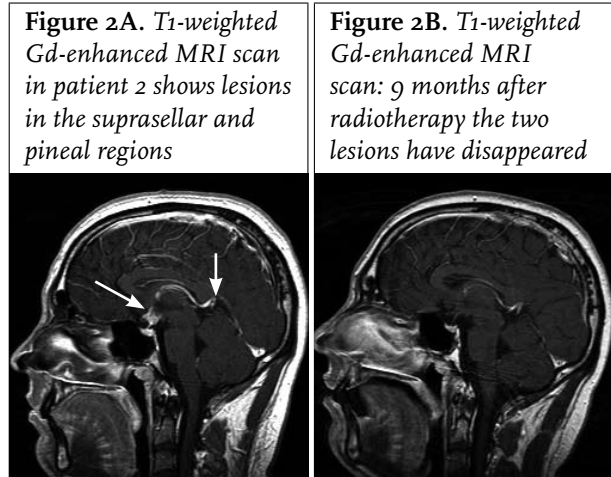
The patient received craniospinal radiotherapy to a dose of 19.8 Gy in 12 fractions, with an additional dose on the pituitary stalk and pineal gland of 21 Gy in 20 fractions. Visual acuity improved gradually. MRI scans of the brain at 3, 6 and 12 months after radiotherapy revealed that the abnormalities at the pituitary stalk and pineal gland had disappeared (figure 1B). At present she is doing well on full hormone replacement therapy. The visual acuity in both eyes is normal.



Case 2

A 23-year-old man was referred to our hospital because of an 18-month history of central diabetes insipidus for which he was treated with nasal desmopressin. MRI scan of the pituitary gland was judged as normal. Six months before referral he complained of fatigue, weakness and erectile dysfunction. He did not complain of headaches or any other neurological symptoms. Physical examination as well as visual acuity were normal. Evaluation of pituitary function revealed panhypopituitarism and hormonal replacement therapy was started. A second MRI scan showed an abnormal aspect of the proximal part of the pituitary stalk. Differential diagnosis included sarcoidosis, germinoma, lymphoma, glioma and histiocytosis X. The patient was referred to our hospital and the MRI was repeated. This MRI showed progression towards the hypothalamic region and a second mass in the pineal gland (figure 2A) The CSF revealed no abnormalities, neither α -fetoprotein nor hCG were present. The clinical picture of diabetes insipidus,

panhypopituitarism and multiple midline lesions was considered compatible with the diagnosis of germinoma. For this reason no biopsy was performed. The patient received craniospinal radiotherapy to a dose of 24 Gy in 12 fractions and an additional dose to the tumours of 16 Gy in 8 fractions. MRI scans of the brain 1, 3 and 9 months after radiotherapy were normal (figure 2B).



DISCUSSION

In this report we present two patients with intracranial multiple midline germinomas in the suprasellar region and pineal gland. In one of the patients the diagnosis was confirmed by histological examination of a biopsy taken from the pineal tumour. In the other patient the diagnosis was made on the basis of the clinical picture and the demonstration of multiple tumours in the midline region with MRI. This diagnosis was not verified by histology. In both cases, the tumours in both regions disappeared after irradiation with a dose lower than usual for intracranial tumours. No recurrence developed during follow-up for more than two years. These case histories raise two questions. Can a diagnosis of multiple midline germinomas be made on the basis of a typical clinical presentation only without histological verification and is a lower dose of radiation than usual for brain tumours indeed justified?

The presenting signs and symptoms of intracranial germinomas depend on the location of the tumour. Intracranial germinomas favour midline structures such as the suprasellar and pineal regions. A suprasellar lesion commonly presents with visual field defects due to compression of the optic chiasm, diabetes insipidus and other signs of hypothalamic-pituitary dysfunction. A lesion in the pineal gland usually presents with neurological dysfunction caused by intracranial hypertension due to direct invasion or obstruction of the CSF outflow,

including headaches, vision abnormalities, papiledema, ataxia, loss of upward gaze, Parinaud syndrome, tremor and altered pupillary reflexes.^{6,7} The differential diagnosis of suprasellar tumours comprises craniopharyngeoma, sarcoidosis, germ cell tumour, histiocytosis X and haemochromatosis. The most common tumours in the pineal region are germ cell tumours and parenchymal tumours such as pineocytoma and pineoblastoma. On the basis of these differential diagnoses of tumours in the suprasellar and pineal regions, the only possible diagnosis in case of multiple midline tumours is a germ cell tumour. Other abnormalities that can occur in the suprasellar region do not occur in the pineal region and vice versa.³

Germ cell tumours can be classified according to their histological picture into pure germinoma, teratoma, embryonal cell carcinoma, yolk sac tumour and choriocarcinoma. The last three types of tumours usually constitute elements of mixed germ cell tumours. Intracranial germ cell tumours contain immunohistochemical features similar to those of gonadal germ cell tumours. These involve hCG, which is present in embryonal cell carcinoma, choriocarcinoma and mixed forms of these, and α -fetoprotein, which is also present in embryonal cell carcinoma as well as in teratoma and yolk sac tumours. These tumour products can also be detected in serum or CSF and are an adjunct to the diagnosis of a germ cell tumour and the prediction of tumour histology.⁸⁻¹⁰ A pure germinoma may contain hCG, but this is usually not the case; α -fetoprotein is not found in pure germinomas. So, in case of intracranial multiple midline tumours with normal values of the tumour markers hCG and α -fetoprotein in serum and CSF the only possible diagnosis is a germinoma. We feel that under such circumstances no histology is required to confirm this diagnosis. This suggestion is in line with published reports of multiple midline tumours in which biopsy revealed the histological picture of germinoma in all cases with normal tumour markers.^{4,5} On the other hand if both hCG and α -fetoprotein are elevated in serum or CSF the only diagnosis is embryonal cell carcinoma. In such a situation a biopsy is not needed either. In the case of elevation of either hCG or α -fetoprotein, there is a differential diagnosis as summarised in *table 1*, necessitating biopsy for histological conformation.

In the first case in this report multiple midline tumours were found which, on the basis of the absence of tumour markers, were expected to be germinomas. The CSF, however, was suspicious for malignancy with lymphocytes positive for cytokeratin, indicating cells of epithelial origin and therefore a biopsy was performed to exclude other tumours than germinoma. Histology, however, showed a histological picture typical for a germinoma. In hindsight, one may wonder whether a biopsy was indicated in this patient,

Table 1. Differential diagnosis of germ cell tumours in relation to tumour markers

	hCG	AFP
Germinoma	±	-
Embryonal cell carcinoma	+	+
Yolk sac tumour	-	+
Choriocarcinoma	+	-
Teratoma	-	+
Mixed	+	-

hCG = human chorionic gonadotropin; AFP = α -fetoprotein

as mentioned before, as in the case of multiple midline tumours without tumour markers the chance of finding a tumour other than a germinoma is less than the risk of a biopsy. In the second patient, a germinoma was considered because of the multiple midline localisations and the absence of tumour markers in serum and CSF and the lack of other abnormalities in the CSF. For the reasons outlined before, a biopsy was therefore not considered necessary to establish the diagnosis and institute radiotherapy. Germinomas are highly sensitive to radiotherapy and survival rates vary between 91 and 97%. Lower dose (25 Gy and a total tumour volume dose of up to 45 Gy) given to the craniospinal axis produces disease-free survival and overall survival equivalent to those seen with higher doses of radiotherapy. Whether or not to radiate the spinal cord depends on the presence of tumour markers in the CSF. If elevated tumour markers are found in the CSF, which may be a sign of dissemination, spinal irradiation is necessary. In other circumstances whole brain radiation is effective in preventing intracranial tumour relapse.¹¹⁻¹³ The reaction to radiotherapy supports the diagnosis: the tumours disappear soon after therapy. This was also the case in our patients. No recurrence occurred during follow-up. This again supports the diagnosis of germinoma as another course would be expected in other types of germ cell tumours after a radiotherapeutic approach.

CONCLUSION

In this report we present two cases of typical multiple midline germinomas. The multiple midline localisations, signs and symptoms of chiasma field defects, pituitary dysfunction and neurological dysfunction favour the diagnosis of pure germinoma. The absence of tumour markers in serum and CSF justifies blind treatment with radiotherapy. Because of the high radiosensitivity of germinomas, low-dose radiotherapy can be used, which is relevant for long-term morbidity as these types of tumours usually arise at a rather young age.

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