CASE REPORT

Unusual behaviour of a pineal germinoma mimicking neurosarcoidosis and metastasising along the endoscopic route

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SUMMARY

A previously healthy man underwent endoscopic biopsy for a suspected pineal germinoma. Histology and immunohistochemistry did not confirm the preoperative diagnosis, and neurosarcoidosis was hypothesised because of the presence of granulomatous reaction. The patient remained in good health for 3 years and was still asymptomatic when a control MRI showed metastasis implantation along the endoscopic route. A redobiopsy provided the diagnosis of germinoma, but was complicated by severe ventricular haemorrhage requiring emergency clot excision. Postoperative clinical conditions were so severe that the treatment of germinoma was postponed. Three months later, repeated MRI showed tumour progression. Chemotherapy promoted good tumour regression so that the treatment was completed by radiation therapy. The tumour completely disappeared on MRI, but the patient remained severely disabled because of the haemorrhage.

BACKGROUND

Pineal germinoma is an uncommon malignant tumour which may favourably respond to chemotherapy and radiation therapy. Granulomatous reaction is rare in intracranial germinoma, but it may be so intense that the typical germinoma cells may be hidden. Even immunohistochemistry may fail if the specimen is small. Adequate biopsy with multiple samples is mandatory, but too insisted or extended biopsies may lead to ominous consequences. Modern neurological assessments now provide high diagnostic accuracy so that the importance of histologically confirmed diagnosis should be not overemphasised.

The possibility that pineal germinoma may be surgically induced to disseminate is taught to each young neurosurgeon. Indeed, this is a quite exceptional event which does not justify the routine enlargement of the radiotherapy field. The present management tendency often prescribes just focal radiation treatment.

CASE PRESENTATION

A precedent healthy 34-year-old man presented with a 2-week history of headache and impaired concentration.

INVESTIGATIONS

An MRI (figure 1) showed triventricular hydrocephalus due to a relatively small space occupying lesion in the pineal region. Such intensely

Figure 1 Initial-enhanced T1-weighted MRI: (A and B) sagittal and coronal views showing a hyperintense tumour of the pineal region which infiltrated the posterior wall of the third ventricle and filled the aqueduct causing obstructive hydrocephalus.

enhancing lesion filled the aqueduct and infiltrated the posterior wall of the third ventricle. Blood tests, serum markers and chest X-ray were normal.

DIFFERENTIAL DIAGNOSIS

Neuroradiological diagnosis was germinoma of the pineal gland. Other embryological pineal tumours were considered less probable, while pineocytomas and gliomas were believed quite unlikely.

TREATMENT

The patient underwent endoscopic third ventriculocisternostomy (ETV) to face with the hydrocephalus,

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and contextual cerebrospinal fluid (CSF) sampling and tumour biopsy. The tumour appeared as a reddish bulging mass on the posterior wall of the third ventricle. Four tissue samples were obtained at different depths, and then the procedure had to be terminated because of tumour bleeding. As a consequence, the specimen was relatively small.

The pathological study revealed an inflammatory process with epithelioid granulomas, without necrosis, but with perivascular lymphocytic infiltration mainly due to T cells (figure 2). Immunohistochemistry showed the negative expression of both the c-kit protein (CD117) and the placental alkaline phosphatase (PLAP). CSF markers were negative too. A diagnosis of probable neurosarcoidosis was given, and the patient was treated by corticosteroids plus immunosuppressive therapy (methotrexate).

OUTCOME AND FOLLOW-UP

Postoperative course was uneventful; the hydrocephalus resulted to be well controlled by the ETV.

Three years later, a completely asymptomatic patient underwent a control MRI (figure 3) which showed minimal progression of the pineal lesion, but implantation metastases along the endoscopic ventriculostomy tract.

The diagnosis of germinoma was reconsidered and a new endoscopic procedure was performed to remove the tract metastases and to have a new biopsy. The pathological studies showed the same tissue in the lesion along the endoscopic route as well as at the pineal level. Again a marked granulomatous reaction was evident, but an island of atypical proliferating cells was now found with positive expression of CD117 but negative of PLAP (figure 4). Accordingly, the diagnosis of pineal germinoma was now possible.

A few hours postsurgery, the patient became deeply comatose with CT scan (figure 5) showing ventricular haemorrhage. Emergency clot evacuation was performed. Postoperatively, the patient remained in a prolonged comatose state and experienced lung infection and sepsis due to *klebsiella pneumoniae*. Chemotherapy and radiotherapy were postponed owing to the severity of the clinical conditions.

Three months later, the patient was awake, but severely obtunded. New MRI (figure 6) showed the recurrence of hydrocephalus and the progression of the tumour. A ventriculoperitoneal shunt was placed and four cycles of etoposide and cisplatin chemotherapy were given. In a couple of months, the tumour

Figure 2 Initial pathological specimen showing an inflammatory process with perivascular infiltration of T-lymphocytes and macrophages and with epithelial not-necrotising granulomas; no neoplasm was evident (H&E, $\times 20$).

Figure 3 Follow-up enhanced T1-weighted MRI obtained 3 years after biopsy and immunosuppressive therapy: (A and B) sagittal and coronal views showing that the hydrocephalus was controlled but the pineal lesion presented slight increase; two hyperintense masses were evident along the endoscopic tract.

markedly reduced and the patient underwent fractionated radiotherapy with 15 MeV electrons with isocentric mesencephalic fields (2 Gy/fr, total dose=24 Gy).

The tumour completely regressed (figure 7). Eighteen months later, the patient is still disease-free, but he remains severely disabled and dependent for most daily activities.

DISCUSSION

Pathological features and bioptic diagnosis

Germinoma is the most common tumour of the pineal region but accounts for less than 1% of all intracranial tumours.^{1 2} It originates from primitive germ cells which fail to migrate to the genital crest during the embryonic life. Cranial germinoma is histologically equal to gonadal seminoma, apart from granulomatous reaction which is relatively frequent in extracranial lesions, but quite unusual in the intracranial ones.^{1 3} Granulomatous reaction depends on the presence of infiltrating T lymphocytes which may produce specific mediators. The granulomatosis cannot be foreseen on MRI, but it may hide the typical large germinoma cells thus seriously hampering the pathological diagnosis. Recently, Schmalisch *et al*¹ reported two cases of pineal germinoma with granulomatous reaction and found only 20 previously reported cases. These authors clearly illustrated the risk of pitfall in endoscopic biopsy: one of their patients was quite similar to ours with the biopsy leading to the

Figure 4 Second pathological specimens: (A) numerous inflammatory cells (lymphocytes) were still present but some aggregates of tumour cells were now evident (H&E, $\times 4\times$); (B) immunohistochemistry showing these neoplastic cells presented marked proliferative activity and positive expression of CD117.

wrong diagnosis of neurosarcoidosis, and germinoma becoming evident only when it progressed. Immunohistochemistry using CD117 and PLAP is usually highly sensitive for germinoma and should be considered in all granulomatous lesions of the cerebral midline.¹⁻⁴ However, cases of false negativity are possible especially when the specimen is small as in some stereotactic or endoscopic procedures.

Cranial germinoma is almost always located in the midline and its more common manifestation is hydrocephalus due to aqueductal occlusion. It generally presents well-defined MRI features which usually evoke a high grade of diagnostic suspicion. Nevertheless, bioptic confirmation is usually considered mandatory. However, despite modern improvements, the pineal region remains one of the more dangerous sites to perform a biopsy because of the risk of haemorrhage.⁵⁻⁶ Granulomatous germinomas have been considered poorly vascularised.¹ However, in our patient, the first bioptic procedure had to be terminated since the tumour tended to ooze; the second biopsy was considered necessary even though the clinical evolution left few doubts about the diagnosis; this time the procedure did not pose particular intraoperative problems, but it was followed by a catastrophic haemorrhage. Now we wonder whether biopsy is really worthwhile when neuroimaging is clear. The importance of pathological confirmation should be carefully weighed up in comparison with the theoretical risks of deciding chemotherapy and radiotherapy basing only on neuroradiological findings.⁷⁻⁸

Figure 5 Emergency CT scan obtained a few hours after the second biopsy showing massive ventricular haemorrhage.

Treatment

In a recent paper, the importance of aggressive surgical removal has been re-evaluated,⁹ but, in general, pineal germinomas associated with hydrocephalus are commonly managed by endoscopic biopsy and ETV, followed by chemotherapy and/or radiotherapy.^{5-6, 10-11} Indeed, it has been reported that the response to radiation therapy would be slower in granulomatous than in non-granulomatous germinomas, but the prognoses of these subtypes remain unclear owing to their rare occurrence.¹⁻³ Our patient well responded first to chemotherapy and then to radiotherapy in spite of the delayed treatment and important tumour progression. The present non-surgical standard of care is cisplatin-based chemotherapy followed by focal radiotherapy.^{7-9, 10-12} However, the optimal radiotherapeutic management still remains controversial.¹² For localised intracranial lesions, no differences would be evident in relapse rates or patterns of relapse when treating with localised radiotherapy alone compared with craniospinal irradiation.¹²

Implantation metastases

In the central nervous system, where endoscopy is a relatively young procedure, implantation metastases have been almost exclusively reported along the needle tract of stereotactic biopsy.¹³ The incidence rate of this complication is unknown, but it is undoubtedly very rare. It would be slightly less uncommon in metastatic tumours.¹¹ A principle long adherent to in neurosurgery is that pineal germinoma may be induced to disseminate by surgical manoeuvres including stereobiopsy. Indeed, this event must be considered almost exceptional.⁵⁻¹¹ We were able to find just one case of pineal tumour with tract recurrence following stereotaxis, but it was a pineoblastoma rather than a germinoma.¹⁴ Unlike stereotaxis, which is a completely intraparenchymal procedure, endoscopic biopsy implies the violation of the ependymal barrier between germinoma and the third

Figure 6 Enhanced T1-weighted MRI obtained 3 months after clot removal: (A and B) sagittal and coronal views showing the progression of the pineal germinoma invading the third and the lateral ventricles.

ventricle. Therefore, CSF dissemination is undoubtedly possible, but there are only two documented cases of germinoma with metastases along the endoscopic route.^{11 13} Metastases may also occur by pulling viable tumour cells into the endoscopic tract during unprotected tissue retrieval or using contaminated instruments.¹³ Anyway, in our patient, the use of an endoscopic sheath did not prevent the implantation.¹³ In the two previously reported cases of germinoma,^{11 13} the interval between biopsy and discovery of the metastases were, respectively, 12 and 17 months. Our patient developed the metastases 36 months after biopsy: perhaps, methotrexate used to treat neurosarcoidosis could have delayed, but not prevented the complication. Both the previously reported patients developed the route metastases despite they had been adequately treated by chemotherapy and radiotherapy after biopsy.^{11 13} Accordingly, we hope that, in our patient, the initial failed diagnosis and the delayed therapy did not play a role in metastases development.

The possibility of implantation tract metastases should be taken into account in the management of pineal germinoma. Theoretically, one could postulate the extension of the field of radiotherapy to include the endoscopic route in order to prevent dissemination.¹³ However, this phenomenon appears so rare that we think such an extension cannot be routinely recommended.

Figure 7 Follow-up enhanced T1-weighted MRI obtained 1 year after chemotherapy and radiation therapy: (A and B) sagittal and coronal views showing the complete tumour regression. The presence of a ventriculoperitoneal shunt was evident.

Learning points

- ▶ Germinoma must be suspected in all intracranial granulomatous lesions of the midline.
- ▶ Pathological diagnosis is important, but in the case of classical neuroradiological features and vascularised tumour, chemotherapy and radiation therapy can be considered even without histological confirmation.
- ▶ The risk of surgically induced dissemination of germinoma is often cited, but it seems a sort of bogeyman for young neurosurgeons and proven cases are exceptional.
- ▶ Modern chemotherapy and radiation therapy regimens may be effective even in much extended diseases.

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