Primary non-gestational mediastinal choriocarcinoma metastatic to the brainstem

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SUMMARY

Choriocarcinoma is a highly malignant tumour emerging from the syncytiotrophoblast divided into gestational and non-gestational presentations. Primary choriocarcinoma of the mediastinum is rare. Metastases to the brain often occur; however, brainstem involvement has not been reported for non-gestational choriocarcinoma. We described a middle-aged man who developed a complete left oculomotor nerve paralysis secondary to a brainstem tumour at the midbrain. The workup for the primary source of the brainstem tumour included a chest CT scan, which revealed a mediastinal mass. A mediastinal mass needle biopsy confirmed the diagnosis of primary mediastinal choriocarcinoma. Despite aggressive chemotherapy, the patient died 6 months after the initial presentation from neurological complications and multiorgan failure.

BACKGROUND

Choriocarcinoma is a highly malignant tumour emerging from the syncytiotrophoblast divided into gestational choriocarcinoma and non-gestational choriocarcinoma. The testis is the most frequent primary site for non-gestational choriocarcinoma, with the mediastinum representing only a small portion.[1 2] Other primary sites include the stomach, liver, lung, brain, small intestine and retroperitoneum.[2 3] Approximately 71%–88% of the patients with primary choriocarcinoma have metastatic lesions when the initial diagnosis is obtained.[2 4–7] The lung is the most frequent metastatic site from primary choriocarcinoma, followed by the liver, brain, retroperitoneum and bone.[2 5] Brain metastases of primary choriocarcinomas are characteristically multiple, frequently with cerebellar involvement.[6 7] Brainstem metastasis from primary non-gestational choriocarcinoma has been previously unreported.

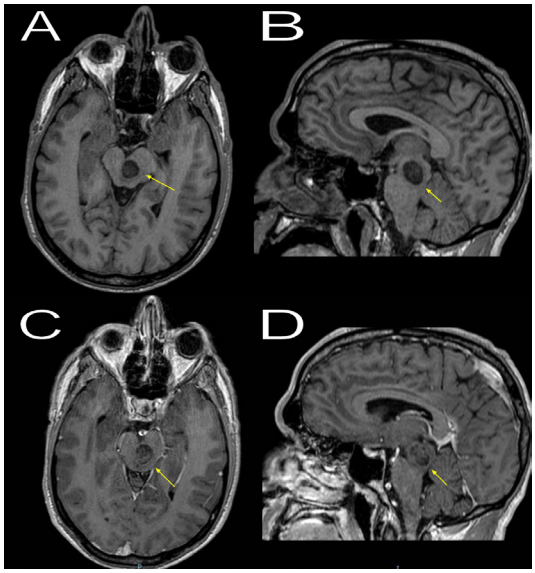

Figure 1 Brain MRI (left: axial, right: sagittal). T1-weighted images without contrast (A,B) and T1-weighted images with contrast (C,D) show a well-defined lesion with mild contrast enhancement at the left midbrain tegmental region (yellow arrow), measuring 1.5 cm anteroposterior × 1.3 cm transverse × 1.9 cm craniocaudal.

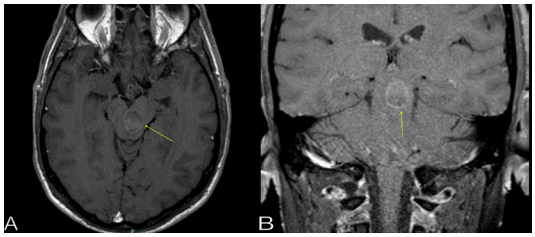

Figure 2 Brain MRI (A) axial and (B) coronal views of the delayed contrast-enhanced T1-weighted images showing contrast rim-enhancement (yellow arrow).

CASE PRESENTATION

A man in his late 40s suddenly developed left ptosis with a lateral and downward deviation of the left eye. He arrived at the emergency department, and the neurosurgery service was consulted. There was no medical history. During the preceding month, he experienced mild headaches, predominantly at night before bedtime. Physical examination showed a complete left oculomotor nerve paralysis. He had no signs of meningeal irritation or papilloedema. The rest of the neurological examination was normal. There were no palpable lymph nodes or masses.

INVESTIGATIONS

Brain MRI showed a well-defined lesion located at the left midbrain tegmental region, measuring 1.5 cm × 1.3 cm × 1.9 cm showing mild contrast enhancement (figure 1). It was hypointense on T1-weighted images and hyperintense on T2-weighted images. The lesion showed no restricted diffusion or susceptibility artefact. Delayed contrast-enhanced T1-weighted images showed rim-enhancement (figure 2). The MRI fluid-attenuated inversion recovery (FLAIR) image had a hypointense signal throughout most of the lesion. Significant contrast enhancement was demonstrated in the contrast-enhanced T2-FLAIR sequence (figure 3). Magnetic

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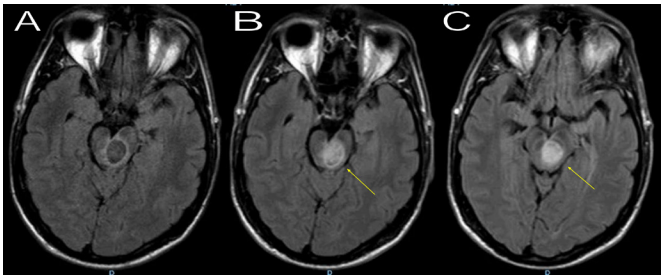

Figure 3 Brain MRI fluid-attenuated inversion recovery sequence. (A) Unenhanced axial view shows mild perilesional oedema, (B,C) Contrast-enhanced axial views show significant contrast enhancement (yellow arrow).

resonance angiography showed a normal cerebral vasculature. The location of the lesion to the left of the midline explained the patient's left third cranial nerve paralysis, as the nucleus and intra-axial portions of the left third cranial nerve were affected. Proton magnetic resonance spectroscopy performed to the midbrain lesion yielded a dominant choline peak with a significant reduction in N-acetylaspartate and an inverted lipid-lactate doublet (figure 4). The choline/creatine ratio was significantly elevated.

Cervical, chest, abdomen and pelvis CT scans with and without contrast were done to evaluate for a primary tumour or other metastatic lesions. The chest CT scan revealed a superomedial mediastinal heterogeneously enhancing mass with cystic/necrotic components, measuring 4.3 cm × 4.5 cm × 8.4 cm (figure 5). The mass was adherent to the right lung but not invading it. A smaller pleural-based pulmonary lesion with an internal cavity was also identified in the right posteromedial lung apex paravertebral region. Multiple enlarged and necrotic mediastinal lymph nodes more prominent in the paratracheal and subcarinal regions were observed. No additional lesions or lymphadenopathy were detected on the abdominopelvic CT scan.

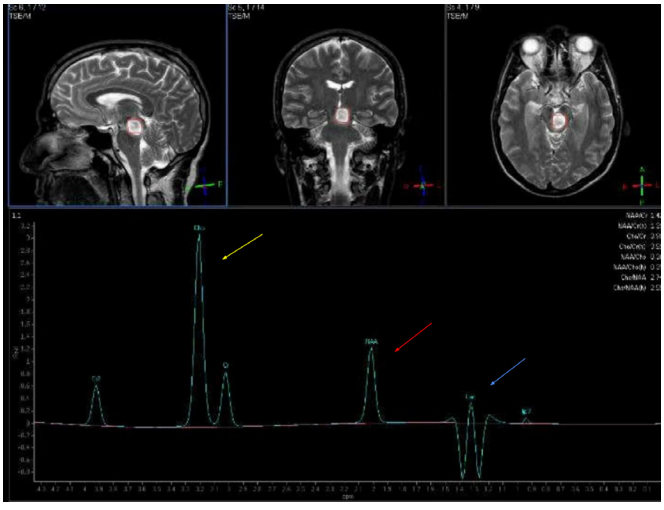

Figure 4 Proton magnetic resonance spectroscopy performed to the enhancing midbrain lesion. A single voxel placed within the midbrain lesion shows an abnormal spectrum with a dominant choline peak (yellow arrow) and a significant reduction in the N-acetylaspartate (red arrow). The choline/creatine ratio of 3.90 is significantly elevated. An inverted lipid-lactate doublet is observed (blue arrow).

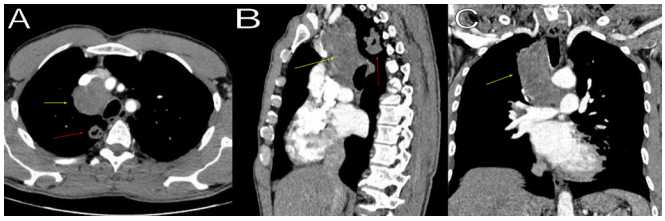

Figure 5 Chest CT scan with intravenous contrast (A) axial, (B) sagittal, (C) coronal images show a superomedial mediastinal heterogeneously enhancing mass (yellow arrow), measuring 4.3 cm anteroposterior × 4.5 cm transverse × 8.4 cm craniocaudal. The mass is adherent to the right lung without invading it. A smaller pleural-based pulmonary lesion (red arrow) with an internal cavity is identified in the right posteromedial lung apex paravertebral region, measuring 3.7 cm × 2.2 cm × 1.9 cm.

DIFFERENTIAL DIAGNOSIS

The patient's complete oculomotor nerve paralysis could be secondary to a vascular lesion compressing the nerve in the subarachnoid space or a lesion compressing the oculomotor nucleus inside the midbrain. The brain MRI findings favoured a neoplastic lesion compressing the oculomotor nerve at the midbrain. Among neoplastic lesions, a diffuse astrocytoma can have a T2-FLAIR mismatch, like in this case, yet it typically does not have the enhancement seen in this case. Therefore, a high-grade neoplasm or a secondary malignant neoplasm was primarily considered. The combination of gadolinium-enhanced MRI findings and the magnetic resonance spectroscopy findings favoured a high-grade neoplastic process given the significant elevation of the choline/creatine ratio and the presence of an inverted lipid-lactate doublet typically indicating necrosis. Further workup was performed to differentiate between a secondary neoplasm or a higher grade primary neoplasm. The chest CT scan revealed a right mediastinal neoplasm; however, a primary bronchogenic carcinoma was unlikely as the mass was only adherent to the lung without invading it. The intrathoracic lymphadenopathy and the midbrain lesion favoured metastatic disease. Our principal differential diagnosis was a primary mediastinal tumour. Although the midbrain lesion could be different from the mediastinal lesion, the presence of intrathoracic lymphadenopathy suggested that the mediastinal mass was the primary tumour with a metastasis to the midbrain.

TREATMENT

The patient underwent a CT-guided needle biopsy of the mediastinal mass. An apical pneumothorax developed after the biopsy, which was treated with a chest tube for 3 days. He was discharged home on the fifth day after the admission. Histopathology and immunohistochemistry of the mediastinal biopsy were compatible with primary mediastinal choriocarcinoma (figure 6). Immunohistochemical stains were positive for human chorionic gonadotropin (hCG), cytokeratin 7 (CK7), tumour protein 63 (p63) and placental-like alkaline phosphatase (figure 7). The Ki67 cell proliferation marker immunohistochemistry was positive in more than 90% of the cells.

Two weeks after the mediastinum biopsy, the patient developed nausea and vomiting and returned to the emergency department. A head CT showed obstructive hydrocephalus secondary to compression of the aqueduct of Sylvius. He underwent an endoscopic third ventriculostomy with complete improvement of the symptoms of hydrocephalus. Given the histopathological findings of the mediastinal biopsy, blood tumour markers were

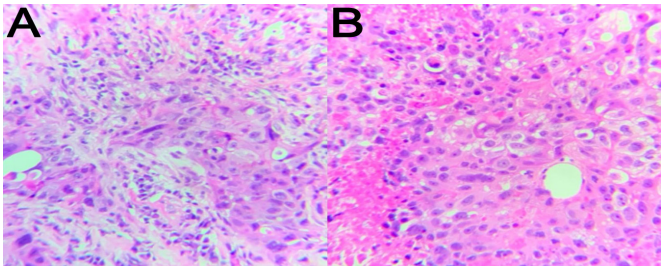

Figure 6 Mediastinal tumour biopsy H&E stain. (A) Tumorous cells composed of atypical syncytiotrophoblasts, cytotrophoblasts and intermediate cells in a solid sheet pattern (100×). (B) Atypical syncytiotrophoblasts, cytotrophoblasts and intermediate cells (200×).

obtained, which showed an elevated hCG level of 85.17 IU/L and a normal alpha-fetoprotein level of 2.2 ng/mL. Scrotal ultrasound showed no intratesticular focal masses.

OUTCOME AND FOLLOW-UP

Three weeks after the endoscopic third ventriculostomy, he was started on chemotherapy protocol (cisplatin, etoposide and bleomycin). Despite four cycles of chemotherapy, his condition worsened, and he died 6 months after the initial presentation from multiorgan failure and neurological complications.

DISCUSSION

In our case, as we did not perform a biopsy of the brainstem lesion, we could be dealing with two different concomitant tumours; however, the large size of the mediastinal tumour with multiple enlarged and necrotic mediastinal lymph nodes suggested that the mediastinal tumour was the primary lesion. The magnetic resonance spectroscopy findings disclosed a midbrain tumour with necrosis similar to the mediastinal mass findings. Primary extragonadal non-gestational mediastinal choriocarcinoma is a highly aggressive tumour primarily seen in young men associated with a poor prognosis.[1–4 8–12] Patients with primary mediastinal germ cell tumours fare worse than those with tumours at other locations.[1 8 9 11 13–17] Malignant germ cell tumours emerge from a totipotent cell; thus, accounting for the wide variety of primary anatomic sites, including gonadal, sacrococcygeal, mediastinal, retroperitoneal and other paraxial locations.[18] Various hypotheses have been proposed to explain the occurrence of extragonadal choriocarcinoma, including an origin from midline primordial cell rests, metastatic choriocarcinoma arising from a resolved gonadal choriocarcinoma or possible transformation from a non-trophoblastic tumour.[3]

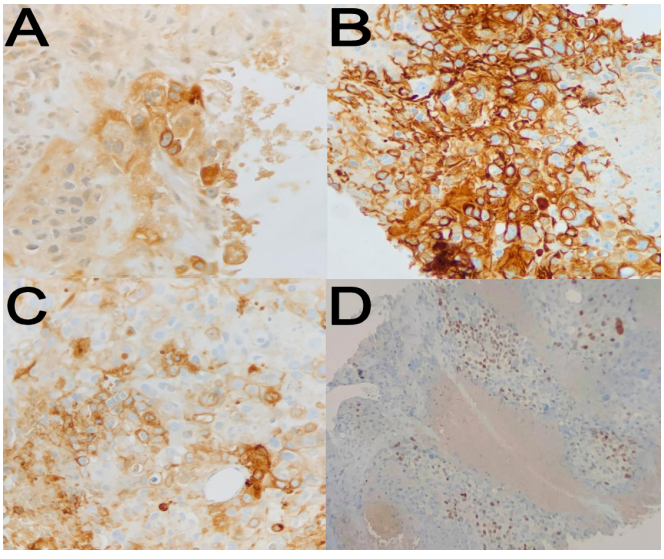

Figure 7 Mediastinal tumour biopsy immunohistochemistry. (A) Focal positivity for human chorionic gonadotropin (200×). (B) Diffuse positivity for cytokeratin 7 (200×). (C) Focal positivity for placental-like alkaline phosphatase (200×). (D) Focal positivity for tumour protein p63 (100×).

It has been long recognised that patients with germ cell tumours who present with brain metastases at diagnosis tend to do better than patients who develop them at relapse.[19–21] However, Feldman *et al* recently showed that in patients with germ cell tumours, multiple brain metastases and the presence of liver or bone metastasis were independent adverse prognostic factors independent of the particular period when the metastases were identified.[10] Mediastinal germ cell tumours present with metastatic disease in 47% of the cases, most frequently to the lungs.[13] Although brain metastases occur in patients with choriocarcinoma, brainstem location is unusual.[22] To our knowledge, only one choriocarcinoma case metastatic to the brainstem has been reported in the literature; however, it involved a primary gestational choriocarcinoma.[23] The patient was a 52-year-old woman presenting 3 years following a miscarriage with an unresectable midbrain tumour. She ultimately died from sepsis and neurological complications.

In patients with a suspected mediastinal germ cell tumour, the diagnosis is usually confirmed using the radiological examinations and measurements of serum alpha-fetoprotein and hCG tumour markers.[12] For patients with secondary brain lesions, needle biopsy to the mediastinum, liver or lymph nodes can be used to establish the correct diagnosis.[9 24] In those cases where the tumour markers are elevated, the brain biopsy can be avoided. Upfront resection of the mediastinal mass should only be attempted in those cases with normal serum markers and if the resection can be performed completely without removing adjoining organs.[18] For primary non-gestational mediastinal choriocarcinoma, the diagnosis relies on radiological examinations followed by biopsy and histochemical staining.[8] In patients with intra-axial brain lesions, contrast-enhanced brain MRI FLAIR images provide better neuroradiological anatomic descriptions.[25 26] In our case, the enhancement of the intra-axial midbrain lesion was more conspicuous using this sequence. Wegman *et al* showed that although immunohistochemical reactivity to hCG was present in 96% of the choriocarcinomas, positive staining also occurred in approximately 50% of other germ cell tumour subtypes, including embryonal carcinoma, yolk sac tumour, seminoma and teratoma.[27] In their study, CK7 and p63 immunostains were superior to hCG to identify

Learning points

- The brainstem represents a site for choriocarcinoma brain metastasis.
- Choriocarcinoma metastatic to the brainstem is extremely rare.
- The prognosis for patients with mediastinal choriocarcinoma metastatic to the brainstem is poor.
- Hydrocephalus may develop from choriocarcinoma metastatic to the brainstem secondary to obstruction of the cerebrospinal fluid pathway.

choriocarcinoma.[27] In our patient, immunostains were positive for CK7 and p63 in addition to hCG.

Brain metastases found synchronous with the choriocarcinoma diagnosis need chemotherapy and radiotherapy, and in some selected cases, surgical removal.[19 20 28 29] Intratumoral haemorrhage is common with brain metastases from choriocarcinoma.[19] Because of the high mortality associated haemorrhage from the brain metastases and the possibility of further haemorrhage induced by chemotherapy, surgical removal of the lesion may be considered a reliable option to prevent cerebral haemorrhage in surgically accessible choriocarcinoma brain metastasis.[30]

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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