CASE REPORT

Metastatic choriocarcinoma induced separate simultaneous intracerebral haemorrhages: a very rare occurrence and its novel association with Klinefelter syndrome

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SUMMARY

Non-traumatic separate simultaneous intracerebral haemorrhages (SSIHs) are rare. Relevant aetiologies are diverse and their diagnosis challenging. We report a unique case of SSIH in an 18-year-old male with a background of previously undiagnosed testicular choriocarcinoma and Klinefelter syndrome. The patient was admitted to Auckland City Hospital with headaches, drowsiness and vomiting. A CT scan revealed SSIH in a background of tumorous lesions. His β human chorionic gonadotropin titre was elevated at 355 000 IU/L. The SSIH and the associated tumorous lesions were acutely surgically resected and the patient started on bleomycin, etoposide and cisplatin combination chemotherapy with excellent results. In this article, we underline choriocarcinoma as a rare aetiology of SSIH and present an example of the clinical presentation, investigation and management of this very rare pathological entity.

BACKGROUND

Separate simultaneous intracerebral haemorrhages (SSIHs) were first described by Tachibana *et al*¹ in 1978 and were subsequently defined as two or more intracerebral haemorrhages (ICHs) affecting different arterial territories with identical computer tomographic density profiles.² Non-traumatic SSIHs are rare and only make up approximately 3% of all ICHs.³ Aetiologies associated with non-traumatic SSIHs include uncontrolled hypertension, vasculitis, sympathomimetic drugs, primary and metastatic brain tumours, cerebral amyloid angiopathy, sinus or cortical venous thrombosis, drug-induced or pathological coagulopathies, posterior reversible encephalopathy syndrome, cavernomas, toxoplasmosis, massive spinal fluid leakage and multiple infarctions (box 1).^{3–6} We report a case of metastatic testicular choriocarcinoma-induced SSIH in a young patient with previously undiagnosed Klinefelter syndrome describing a potentially curative form of management and evidencing a novel concomitance of disease between an extremely rare medical occurrence and a genetic disorder.

CASE PRESENTATION

An 18-year-old man presented to the emergency department with a frontal headache, vomiting, drowsiness and confusion. His admission vital signs were unremarkable, admission Glasgow Coma

Scale (GCS) was 14 (M6E4V4) and he did not display any focal neurological deficits.

The patient's medical history was notable for lifelong learning difficulties and behavioural problems, alcohol, tobacco and marijuana abuse, right-sided blindness attributable to a previous traumatic eye injury, migraines, recent episodes of left eye posterior scleritis and the recent development of bilateral gynaecomastia and testicular atrophy. No family history of interest was noted.

A head CT scan revealed distinct multicentric foci of cerebral haemorrhages in the right frontal and parietal lobes measuring 4 and 5.5 cm in maximal diameter, respectively (figure 1). The haematomas were associated with marked mass effect and early hydrocephalus.

MRI subsequently confirmed the CT findings and further characterised the haemorrhages as intratumoral.

The full blood count displayed a leucocytosis (17.92 E+9/L) and a neutrophilia (16.75 E+9/L). C reactive protein was mildly elevated at 8 mg/L. Serum chemistry was normal. β Human chorionic gonadotropin (B-HCG) was extremely elevated at 355 000 IU/L. α Fetoprotein was not elevated.

One day later, while being observed in the neurosurgical high dependency unit awaiting a staging CT of the chest, abdomen and pelvis along with a testicular ultrasound, the patient

Box 1 Differential diagnosis of non-traumatic separate simultaneous intracerebral haemorrhages (SSIHs)

Aetiology

- Hypertension
- Vasculitis
- Cerebral amyloid angiopathy
- Sympathomimetic drug use
- Primary and metastatic brain tumours
- Sinus or cortical venous thrombosis
- Drug-induced or pathological coagulopathies
- Toxoplasmosis
- Haemorrhages due to massive spinal fluid leakage
- Cavernomas
- Posterior reversible encephalopathy syndrome
- Multiple infarctions

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Figure 1 Separate simultaneous intracerebral haemorrhages on axial head CT head imaging. (A/B) Axial frames of the patient's preoperative head CT taken through the maximal diameter of the right frontal (A) and right parietal (B) haemorrhage demonstrating two distinct multicentric foci of cerebral haemorrhage in the right frontal (white arrow in frame A) and parietal lobes (white arrow in frame B), respectively, measuring 4 and 5.5 cm at their maximal diameter. The right frontal haemorrhage shows a 6 mm nodule of arterial phase enhancement possibly demonstrating a spot sign. No associated enlarged venous pedicles suggestive of an arteriovenous malformation are seen. The haemorrhages are associated with a marked mass effect and a midline shift to the left of 14 mm. Early hydrocephalus is noted. C/D: Axial frames of the patient's day 4 postoperative CT head taken at the same level as frame A (C) and frame B (D) demonstrating postoperative changes in the right frontal and right parietal lobes with no residual tissue and no hydrocephalus. Intraventricular air and residual midline bowing to the left is noted. (E/F) Axial frames of the patient's postchemotherapy head PET-CT taken at the same level as frames A and C (E) and frames B and D (F). The scans demonstrate postsurgical changes in both resected regions with the focus within the right parietal region demonstrating some gliosis and ex-vacuo dilation of the occipital horn of the right ventricle. A faint attenuation in metabolic activity is evidenced in the surgically resected areas in keeping with the postsurgical changes. No focal increase in metabolic activity is noted.

experienced a deterioration in his GCS to 7/15 (M5E1V1). His left pupil became fixed and dilated. Given his acute neurological deterioration with evidence of raised intracranial pressure, he was emergently intubated and transferred to the operating room for an emergency decompressive craniotomy, evacuation of intracerebral haematomas and resection of the right frontal and parietal lesions. There were no immediate perioperative or intraoperative complications.

Following the operation, he was noted to have a left hemianopia and his postoperative day 4 head CT demonstrated postoperative changes in the right frontal and parietal lobes with no definite residual tissue ([figure 1](#)).

Histology from the resected brain lesions confirmed metastatic choriocarcinoma, and a subsequent CT scan of the chest, abdomen and pelvis revealed widespread mediastinal and pulmonary disease. A testicular ultrasound demonstrated a 4–5 mm hypoechoic lesion of the right testis. The patient opted not to undergo an orchidectomy, but this was presumed to be the primary cancerous locus.

The patient was later transferred to the department of medical oncology for chemotherapy where his initial assessment confirmed testicular atrophy and bilateral gynecomastia and revealed elevated serum testosterone and oestradiol titres. He was subsequently formally diagnosed with Klinefelter syndrome on the basis of a fluorescent in situ hybridisation chromosomal analysis. The patient was started on a chemotherapy regime of bleomycin, etoposide and cisplatin combination chemotherapy (BEP) with curative intent.

This management displayed immediate efficacy in reducing the patient's B-HCG levels.

OUTCOME AND FOLLOW-UP

Four months after presentation, following one cycle of etoposide and cisplatin (EP) combination chemotherapy and four cycles of BEP, the patient's B-HCG levels had fallen to 19 IU/L ([figure 2](#)). A brain positron emission tomography CT scan and spinal MRI scan showed no residual disease ([figure 1](#)) and it was at that point believed that chemotherapy, in conjunction

Figure 2 Serial serum β human chorionic gonadotropin (B-HCG) assays and their relation to chemotherapy cycles.

with a surgical orchidectomy, would achieve a complete cure. Unfortunately, the patient later declined treatment for pneumonia superimposed on a background of bleomycin pneumonitis and died at home.

DISCUSSION

Our patient presented with non-specific symptoms of increased intracranial pressure classically attributable to space occupying lesions. Radiological investigations evidenced SSIH of unclear aetiology. In the absence of trauma, uncontrolled hypertension or a hypertensive event account for the majority of SSIH cases. These aetiologies were deemed unlikely on the basis of the patient record and cerebral amyloid angiopathy was thought unlikely due to the patient's young age. The structurally abnormal brain parenchyma surrounding the haemorrhage, in addition to the patient's extremely elevated B-HCG, supported the histological diagnosis of a neoplastic haemorrhage.

Metastatic choriocarcinomas have previously been described as prone to massive intracranial bleeding.⁷ Kidd *et al*⁸ described them in relation to non-simultaneous multiple ICHs and Nishizaki *et al*⁹ associated them with SSIH reporting the case of a 24-year-old male who experienced three concomitant bleeds from metastatic choriocarcinoma tumours in the right frontal and parietal lobes. This case, which is, to the best of our knowledge, the only other case to describe choriocarcinoma-induced SSIH, interestingly mimics the exact haemorrhage distribution of our patient.

The reported incidence of germ cell tumours in patients with Klinefelter syndrome is 1.5/1000, a 50-fold increase over the general population.¹⁰ This association, of which the exact basis is still not understood, may underlie the presence of a metastatic

choriocarcinoma, an extremely rare neoplasm accounting for only 0.3% of all non-seminomatous germ cell tumours,¹¹ in our patient. This present account is, to the best of our knowledge, the first to associate choriocarcinoma-induced SSIH with Klinefelter syndrome.

BEP is a standard chemotherapy regimen for advanced testicular cancers and has been shown to be effective in the management of testicular choriocarcinoma with lung

Learning points

- ▶ Separate simultaneous intracerebral haemorrhages (SSIHs) are rare, present with non-specific symptoms of increased intracranial pressure and require radiological investigation for diagnosis.
- ▶ SSIH aetiologies are diverse and their diagnosis and management challenging, but, in the absence of trauma, uncontrolled hypertension or hypertensive events account for the majority of cases.
- ▶ Primary and secondary neoplastic lesions have been associated with SSIHs; metastatic choriocarcinoma is now underlined as a validated aetiology and the novel association of SSIH, testicular metastatic choriocarcinoma and Klinefelter syndrome has been reported in a patient.
- ▶ Together, acute surgery and bleomycin, etoposide and cisplatin combination chemotherapy combination chemotherapy display life-saving and curative potentials in management for metastatic choriocarcinoma induced SSIH.

metastases.^{12 13} In our case, the combination of acute surgery and BEP was shown to have life-saving and curative potential in the treatment of SSIH and of the causative testicular choriocarcinoma with brain metastases.

Separate spontaneous ICHs are a rare clinical entity. In this unique case, we report on the interesting presentation, investigation and management of separate spontaneous ICHs and underline metastatic choriocarcinoma as a rare aetiology, as well as demonstrating the potentially curative character of surgery and combination chemotherapy as a management. Moreover, we describe the previously undescribed association between choriocarcinoma-induced SSIH and Klinefelter syndrome.

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