Rare disease

Bronchogenic adenocarcinoma presenting as a synchronous solitary lytic skull lesion with ischaemic stroke – case report and literature review

David O'Connell,¹ Chandrasekaran Kaliaperumal,¹ Gerald Wyse,² Julie McCarthy,³ Aisling Ryan⁴

¹Department of Neurosurgery, Cork University Hospital, Cork, Ireland;

²Department of Neuroradiology, Cork University Hospital, Cork, Ireland;

³Department of Pathology, Cork University Hospital, Cork, Ireland;

⁴Department of Neurology, Cork University Hospital, Cork, Ireland

Correspondence to Mr Chandrasekaran Kaliaperumal, ckaliaperumal@gmail.com

Summary

The authors describe a rare case of metastatic bronchogenic adenocarcinoma in a 55-year-old man presenting with concomitant solitary lytic skull lesion and ischaemic stroke. Metastatic bronchogenic carcinoma is known to present as lytic skull lesions. Primary brain tumours are also known to cause ischaemic brain injury. An underlying stroke risk may be exaggerated by cranial tumour surgery. Patients with brain tumours are well known to be predisposed to an increased risk of developing thromboembolic disease. It is unusual to see metastatic bronchogenic adenocarcinoma presenting as ischaemic stroke with a background of concomitant cerebral metastasis. The aetio-pathogenesis of this rare occurrence is discussed with a review of literature.

BACKGROUND

It is very rare for lung tumours to present as brain metastasis associated with an underlying ischaemic stroke. Primary brain tumours are well known to cause ischaemic stroke unlike metastatic tumours.^{1–3} We describe this rare occurrence of metastatic bronchogenic adenocarcinoma presenting as a lytic lesion with a synchronous ischaemic stroke. The patient was initially referred from accident and emergency as ischaemic stroke and subsequent investigation revealed a skull lytic lesion.

CASE PRESENTATION

A 55-year-old man, presented with bilateral upper limb weakness, associated with decreased sensation over a period of 3 weeks. He also experienced right upper limb numbness and weakness acutely which has persisted since. He had associated nausea and vomiting for a week prior to admission and reported a weight loss of one stone in 3 weeks. His medical history included diet controlled diabetes mellitus and chronic obstructive airways disease. He is an ex-smoker with a 75-pack year history and was previously a heavy alcohol consumer.

On examination, his pupils were unequal, left pupil size 5 mm and right pupil size 3 mm, and reactive. A right inferior quadrantanopia was noted. His extra ocular movements were intact and the rest of his cranial nerve examination was normal. He had moderate weakness of his right upper limb and right lower limb of grade 3/5 associated with brisk reflexes with an upgoing plantar reflex. He had right-sided supraclavicular lymph node enlargement. Laboratory testing was insignificant other than an increased C-reactive protein of 88.8. Chest x-ray showed a small left-sided pleural effusion and a small round right mid zone mass lesion, which was not present

in the chest x-ray, performed in 2008. CT brain (figures 1 and 2) showed a large low attenuation area in the left frontoparietal region extending to the left temporal lobe with contrast enhancement. There was erosion of the overlying left parietal bone. MRI brain (figures 3 and 4) showed an area of predominantly cortically based abnormal signal with well-defined margins in the left cerebral hemisphere, extending over a distance of 9.3 cm in anteroposterior direction, involving posterior aspect of the frontal lobe and also temporoparietal lobes. Vascular flow voids were seen to course through this mass especially at the superior aspect. There was no evidence of intralesional haemorrhage. These features were in keeping with a locally advanced neoplastic lesion with local bony erosion. Diffusion weighted imaging (DWI) revealed frontoparietal ischaemic infarct extending into the temporal operculum and involving the posterior aspect of the insula (figure 5).

INVESTIGATIONS

A CT scan of thorax, abdomen and pelvis was subsequently performed with oral and intravenous contrast, showing a right lower lobe nodule, suspicious for primary lung cancer, and extensive right hilar and contralateral mediastinal lymphadenopathy (figure 6). Adrenal metastases were noted with the above findings. A right-sided supraclavicular lymph node aspirate was performed under ultrasound guidance, which showed clusters of malignant glandular epithelial cells displaying polymorph emperipolesis consistent with a metastatic adenocarcinoma. Immunostaining was performed, which was positive for CK7 and negative for CK20, prostatic specific antigen, thyroid transcription factor-1/Napsin suggesting a primary site within the upper gastrointestinal tract or lung (figure 7a,b).

Figure 1 Axial CT brain with lytic skull lesion and underlying ischaemia.

Figure 2 Axial CT-bone window demonstrating moth eaten appearance in the skull vault.

Figure 3 T1 weighted axial post contrast MRI.

Figure 4 T2 weighted axial MRI.

Figure 5 Diffusion weighted imaging demonstrating restriction of diffusion suggesting stroke.

Carotid ultrasound Doppler was performed which showed no significant stenosis in either internal carotid artery (ICA). Definitive diagnosis was of concomitant brain metastases with ischaemic stroke. With this clinical picture he was planned for whole brain radiotherapy and he has completed the radiotherapy.

DIFFERENTIAL DIAGNOSIS

- ▶ Ischaemic stroke
- ▶ Metastasis
- ▶ Plasmocytoma (multiple myeloma).

TREATMENT

The patient was referred to radiation oncology for whole brain radiation. He is also due for chemotherapy and radiotherapy for his lung lesion.

DISCUSSION

In the developed world, cerebrovascular disease is the second most frequent cause of death and respiratory tract cancers are the third most common cause of death.⁴ Cerebrovascular disease is the most frequent neurological disease. The prevalence of lung cancer is second only to that of prostate cancer in men and breast cancer in women, and lung cancer is the most common cause of cancer-related deaths, responsible for 1.4 million deaths in 2008 alone.⁵ Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. The most frequent subtype in USA being adenocarcinoma, which accounts for 35–40% of all lung cancers.

Figure 6 CT thorax demonstrating the lung lesion (arrow) and mediastinal lymphadenopathy.

Several review articles have been published so far explaining the link between neoplastic disease and the development of cerebrovascular accidents. Ischaemic stroke in particular has been extensively reviewed. MRI, especially DWI and apparent diffusion coefficient is an essential prerequisite to delineate ischaemic change in stroke patients. Stroke may be the first sign of cancer, leading to its detection, but this is a rare occurrence.⁶ Stroke occurs more frequently in patients with cancer than in the average population.⁷ More recent studies report a very similar incidence between cancer and non-cancer patients. Approximately 15% of the patients with cancer have cerebrovascular disease and the frequency of occurrence cerebral infarcts is similar to that of intra cerebral haemorrhage.⁸ Despite the trend towards similar incidence and risk profile for both groups, several cancer specific aspects need to be considered.⁹ Table 1 summarises the possible aetiologies for pathogenesis of stroke in malignancy. The aetiology is discussed briefly below.

Direct tumour effect

Tumour embolism may be considered as a direct cause of cancer causing stroke. Tumours may also cause stroke by direct vessel compression or by compression and invasion of large arteries resulting in cerebral infarction.

Coagulation disorders

Several acquired prothrombotic states are associated with an increased risk of stroke. These include cancer, myeloproliferative disorders, the antiphospholipid syndrome and heparin-induced thrombocytopenia. Cerebral venous

Figure 7 (a) May–Grunwald staining demonstrating small lymphocytes and cohesive larger tumour cells. (b) CK 7 antibody stain identifying tumour cells (brown).

Table 1 The possible aetiologies for pathogenesis of stroke in malignancy

Mechanisms of stroke in patients with cancer
Tumour related
Direct tumour effect
Intravascular lymphoma
Haematological malignancies
Coagulation disorders
DIC
Non-bacterial thrombotic endocarditis
Infection
Therapy related
Radiotherapy
Chemotherapy
Miscellaneous
DIC, disseminated intravascular coagulopathy.

thrombosis, venous thromboembolism and Trousseau syndrome are more common in patients with solid tumours, whereas disseminated intravascular coagulopathy (DIC) is more frequent in metastatic cancer. DIC in patients with cancer can be associated with thrombotic stroke and with intracerebral haemorrhage.¹⁰ Non-bacterial thrombotic endocarditis (NBTE) is thought to be one of the most common causes of ischaemic stroke in patients with cancer.¹¹ In a large autopsy series of 171 cases of NBTE, 59% of patients suffered from malignancy. In NBTE, sterile vegetations, located on cardiac valves, cause embolisation into the arterial system and brain. This may occur in association with DIC. Other coagulation disorders associated with stroke in patients with cancer include acquired protein S deficiency, protein C deficiency, activated protein C resistance and presence of antiphospholipid antibodies.

Infection

Central nervous system infections in patients with cancer may present similarly to strokes. Patients with cancer and haematological malignancies are often immunologically compromised and immunity may be further suppressed by radiotherapy and chemotherapy, allowing the development of opportunistic infections for example, JC-40 virus and fungal infections.¹² Reactivation of Varicella-Zoster infection is common and may be complicated by encephalitis.¹³ Sepsis may occur and be associated with DIC.

Therapy-Related

Therapy-related strokes can occur in three categories:

- In association with surgery – surgery may provoke the release of emboli. Strokes have been described perioperatively and postoperatively during pulmonary interventions such as bronchoscopic biopsy.^{14 15}
- In association with radiotherapy – The most common postradiation complication is vasculopathy of medium and large sized vessels. The frequency of ICA stenosis post external neck radiation ranges from 12 to 60%. In children, whole brain radiotherapy may result in the development of Moya Moya disease. ‘Stroke-like’ migraine attacks after radiotherapy generally have a good prognosis but may persist for several days. Following neck radiotherapy, pseudo-aneurysm formation and rupture of carotid arteries may occur and has been characterised as carotid blow-out syndrome.¹⁶
- In association with chemotherapy – conflicting research supports the theory that several chemotherapeutic agents may pose a risk for stroke. A study of 10 963 patients in 2006 concluded that the risk for stroke was predicted by the use of cisplatin-based chemotherapeutic agents rather than by the histological type of cancer. However, other studies do not reach the same conclusion. Cisplatin and gencitabine, when used in the treatment of NSCLC, seem to be a powerful risk factor for vascular events.¹⁷ Intrathecal administration of methotrexate may also be associated with stroke-like events or strokes.¹⁸ Although the association between chemotherapeutic agents and stroke, seems to be strongest with cisplatin, methotrexate and L-asparaginase-containing regimens, systemic usage of cyclophosphamide, 5FU, taxol and paclitaxel have been reported to be associated with stroke.¹⁷

Miscellaneous

Colony-stimulating factors for example, erythropoietin and granulocyte CSF are considered to be beneficial in stroke management.¹⁹ Other drugs for example, all-trans retinoic acid and corticosteroids are reported to have thrombogenic potential²⁰ which can potentially lead to stroke. Influence on stroke of new biological cancer therapies for example, antibodies, has not yet been systemically studied.

Bronchogenic adenocarcinoma can present with metastases including multiple skull lytic metastases. It is however,

unusual to present with stroke-like symptoms with radiologic appearance synchronously. Our patient described, had several risk factors putting him at risk of developing cerebrovascular disease and, one may argue, that these occurrences could be two separate pathologies occurring simultaneously. On analysing the history, examination and the radiological findings we are able to conclude that the overall presentation is highly suggestive of a metastatic lesion causing a subacute ischaemic event.

Learning points

- We conclude that this is a rare occurrence.
- The underlying ischaemic insult due to metastasis should be managed with palliative radiotherapy to the brain apart from the treatment of the primary lung adenocarcinoma.
- MRI DWI is recommended as a part of the investigation to determine the nature of the brain lesion apart from CT brain (pre and post contrast) and staging CT of whole body.

Competing interests None.

Patient consent Obtained.

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