

CASE REPORT

Multiple embolic cerebral infarcts as the first manifestation of metastatic ovarian cancer

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SUMMARY

A 36-year-old woman presented to the emergency department with a 3-day history of an occipital headache associated with transient visual impairment and short-term memory loss. MRI of the brain showed innumerable focal embolic infarcts of differing ages, for which a cause could not be determined. The patient was discharged and readmitted 7 weeks later with acute aphasia and a right-sided hemiplegia. CT of the abdomen revealed a right-sided ovarian mass and prominent retroperitoneal nodes, which cytology confirmed to be metastatic ovarian cancer.

BACKGROUND

Our case is important because it highlights the need for investigating young patients with cryptogenic stroke for an underlying malignancy.

CASE PRESENTATION

A 36-year-old woman attended the emergency department with a 3-day history of a mild occipital headache associated with nausea, diarrhoea and photophobia, a transient visual impairment in her right eye and vague short-term memory loss. At the time of her presentation to the emergency department, all of her symptoms had fully resolved.

The patient denied any recent illnesses or a history of migraines. She had no medical history or hospital admissions and her only regular medication was an contraceptive pill. She was a non-smoker and happily married with three young children. Her family history was unremarkable, with no history of malignancy or neurological disorders.

Her vitals were stable and her initial physical examination, including a full neurological examination, was normal.

INVESTIGATIONS

Haematological, biochemical, protein analysis, vasculitic screen and serology investigations were all normal apart from a mildly raised C reactive protein of 25.4 mg/L.

CT of the brain was normal; however, MRI showed multiple tiny, subcentimetre foci of increased signal on T2-weighted image and fluid-attenuated inversion recovery imaging. These foci were located in the left hippocampus, left cerebellar hemisphere, left thalamus, right parietal, and right and left frontal lobes. The areas of increased signal were innumerable and reported to be focal, embolic infarcts (figure 1).

After discussion with the cardiology services, a transoesophageal echocardiogram (TOE) was

performed as it has the highest specificity towards detecting cardiac abnormalities or vegetation as the causes of embolic infarcts. The TOE showed no cardiac thrombus, atrial septal defect or patent foramen ovale. There was normal biventricular function with a mild-to-moderate mitral regurgitation and no vegetation seen on the cardiac leaflets. In addition, the patient's 24 h Holter monitor, carotid ultrasound (US) with Doppler imaging, vasculitic screen and lumbar puncture were all unremarkable. Further radiological investigations, including cerebral angiography and a CT angiogram of her intracranial structures, were also normal.

DIFFERENTIAL DIAGNOSIS

Our patient had multiple embolic infarcts of differing ages, confirmed by an MRI of the brain. Taking the patient's age into consideration, our main differentials were either a cerebral vascular abnormality, or a cardiac abnormality, as the underlying cause for her cerebral infarcts. During our extensive stroke work up, our investigations showed no convincing evidence for either of these. At the time of discharge, the patient was diagnosed with multiple embolic infarcts of unknown aetiology.

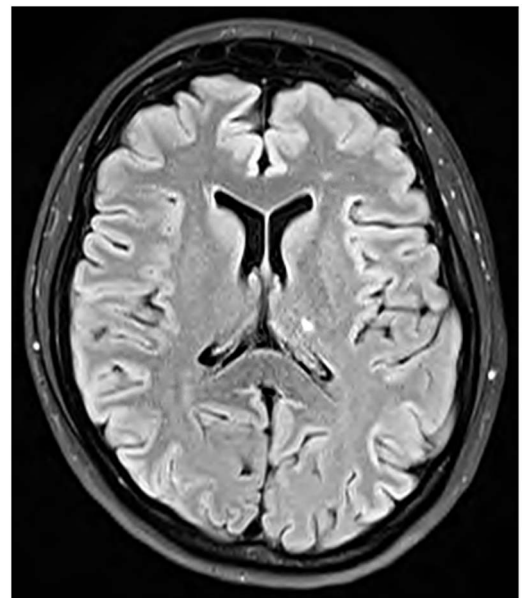


Figure 1 Brain MRI showing multiple tiny, subcentimetre foci of increased signal on T2-weighted image and fluid-attenuated inversion recovery imaging. These foci are located in the left hippocampus, left cerebellar hemisphere, left thalamus, right parietal, and right and left frontal lobes. The areas of increased signal are innumerable and represent focal, embolic infarcts.



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TREATMENT

The patient was discharged on day 10 and started on aspirin 150 mg once daily. Her follow-up included urgent neurology and stroke outpatient review. Unfortunately, the patient had to re-represent to hospital before attending her outpatient appointments.

OUTCOME AND FOLLOW-UP

Seven weeks after her first presentation, the patient was readmitted with an acute episode of aphasia and right-sided hemiplegia. Her National Institutes of Health Stroke Scale (NIHSS) on admission was 18. CT of the carotid arteries and intracranial vasculature showed two foci of embolic or thrombotic occlusion within the proximal anterior and posterior divisions of the left middle cerebral artery, just beyond the left distal M1 and left M2 bifurcation. There was excellent collateralisation throughout the left cerebral hemisphere, close to 100% when compared with the right cerebral hemisphere. Tissue plasminogen activator (tPA) was started as the patient was <3 h post-cerebrovascular accident event, and, in addition, the patient underwent a successful cerebral artery thrombectomy under interventional radiology guidance, with good motor recovery but persistent expressive aphasia.

The patient underwent a repeat TOE, which showed normal biventricular function, and no atrial septal defect, patent foramen ovale or thrombus. There was moderate-to-severe mitral regurgitation with thickened mitral valve leaflets and diffuse echodensities on both leaflets, with elevated estimated pulmonary pressures.

On day 2 of her second admission, the patient reported severe bilateral lower limb pain and abdominal discomfort with bruising over both shoulders, possibly a side effect from the tPA treatment. CT of the abdomen and pelvis showed a 6.4×3.9 cm solid and cystic right ovarian mass, prominent calcified retroperitoneal nodes and masses, scattered calcified small nodes in the retrocrural and left para-aortic regions, and a moderate volume of free fluid in the pelvis. Better views and more diagnostic information were also gained with dedicated US sonography of the ovaries (figure 2). The patient's cancer antigen 125 (CA-125) level was 2350, and cytology and fine-needle aspiration of her left axillary lymph node showed features of metastatic adenocarcinoma.

She was diagnosed with metastatic ovarian cancer on day 2 of her second admission. As the patient had numerous complex medical issues, she was deemed unsuitable for surgery, and the management plan was for ongoing palliative team input and for

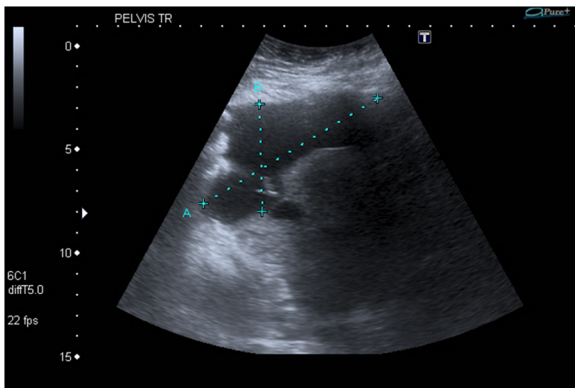


Figure 2 Ultrasound of the right ovary showing a 6.4×3.9 cm solid and cystic right ovarian mass.

the patient to undergo three cycles of paclitaxel and carboplatin chemotherapy every 3 weeks. The patient received one cycle of chemotherapy on day 33 and passed away on day 54 of the second admission, an autopsy was declined by her family.

A histology specimen of the ovary was not obtained and therefore we cannot with full certainty comment on the type of ovarian primary; however, on the basis of the cytology, it is most likely of a papillary serous nature, the International Federation of Gynaecologists and Obstetricians (FIGO) stage IVB.

DISCUSSION

Thromboembolic events are well known yet devastating complications of malignancy. The association between cancer and thrombosis was first described in 1865 by Armand Trousseau after noting that certain patients who presented with unexpected or migratory thromboses were later found to have a visceral malignancy.¹ Over the years, clinicians have defined and expanded the term ‘Trousseau’s syndrome’ to describe ‘unexplained thrombotic events that precede the diagnosis of an occult visceral malignancy or appear concomitantly with the tumour’.²

Ovarian cancer is associated with one of the highest incidence rates of venous thrombosis.³ In addition, a recent nationwide population-based study found that patients with ovarian cancer are also at increased risk of developing ischaemic stroke, with an adjusted HR of 1.49.⁴ Cerebral infarction, besides having a huge impact on a patient’s quality of life, also increases mortality rates, with one study reporting a median survival of 4.5 months among patients with cancer following an ischaemic stroke.⁵

Risk factors associated with stroke in patients with ovarian cancer include age ≥50 years, diabetes mellitus, hypertension and chemotherapy treatment.⁴ As with our patient, up to 40% of strokes in cancer are considered to be ‘cryptogenic’.⁶ Cryptogenic stroke can be defined as brain infarction not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac and serological evaluation, and is suggestive of a direct link between cancer and ischaemic stroke through various molecular mechanisms.

One of the most well-documented mechanisms linking cancer and stroke is the hypercoagulability of patients with cancer. Patients with cancer with cryptogenic stroke have been found to have higher D-dimer levels compared to patients with stroke without malignancy,⁷ a finding consistent with our patient. Although a number of cancers have been associated with a hypercoagulable state, adenocarcinomas have been significantly associated with cancer-related stroke.⁸ Adenocarcinomas are known to secrete the high-molecular-weight molecule, mucin, into the bloodstream, which can precipitate a viscous and hypercoagulable state, and interact with leucocyte and platelet selectins, inducing the formation of platelet-rich microthrombi.⁹ We can hypothesise that this mechanism could have played a role in the pathogenesis in our patient, as her tumour was later confirmed to be of the adenocarcinoma type.

Tumour cells have also been reported to produce a number of procoagulants including tissue factor,¹⁰ cancer procoagulant (CP)¹¹ and inflammatory cytokines. Secreted tissue factor binds to factor VIII to potentiate the clotting cascade and thereby thrombosis.¹⁰ CP activates factor X to generate thrombin and is not dependent on the factor VII/tissue factor complex.¹² Malignant cells are also known to secrete inflammatory cytokines including tumour necrosis factor- α , interleukin 1 (IL-1) and IL-6. These cytokines cause sloughing of the endothelial

cells and increased blood sludging, as well as inducing tissue factor in cancer cells, to potentiate the coagulation cascade.¹³ In addition, they also inhibit protein C activation, which normally acts as one of the main anticoagulant defence systems.¹⁴ Pathological platelet activation with reduced sensitivity to prostacyclin, increased aggregability and higher levels of platelet-specific product soluble, P-selectin, which is the largest of the known selectins at 140 kDa, platelet factor 4, thrombospondin and β -thromboglobulin, have also been associated with cancer-related stroke including ovarian malignancy.¹⁵ Our patient exhibited thrombocytopenia during her second admission and this has been documented in a similar case.¹⁶

There are other mechanisms that link cancer to stroke and these have been documented in other case reports of ovarian cancer presenting as cerebral infarction.^{17 18} They include non-bacterial thrombotic endocarditis, where sterile vegetations grow on the aortic and/or mitral valve, and are thought to be composed of disrupted fibrin and platelets, and are susceptible to embolisation.¹⁷ TOE is accepted as the modality of choice to detect these vegetations and was included in part of the work up in our patient.

In addition, paradoxical emboli is a term given to venous clots that lead to stroke following venous-to-arterial shunting, which may occur via a patent foramen ovale.¹⁸ Direct tumour compression of blood vessels from primary brain tumours or brain metastases leading to cerebral ischaemic and subsequent infarcts has also been implicated in cancer-related stroke,¹⁹ as well as the direct effect of cancer-associated treatments such as cisplatin, methotrexate and L-asparaginase, which, though poorly understood, are thought to be related to venous and arterial thromboembolic events.²⁰

As cryptogenic stroke has been found to be a manifestation of occult malignancy, it may be useful to have a number of screening techniques including D-dimer levels, of which elevated levels may raise suspicion of an underlying malignancy; tumour markers such as CA-125, which is elevated in patients with ovarian cancer and was indeed significantly elevated in our patient; breast and testicular examinations; CT of the chest, abdomen and pelvis; and, in high risk women, consideration of a transvaginal US.⁹ There is a question as to whether the early detection of stroke-related malignancy improves patient outcomes. Cerebral infarction has been documented in a number of studies in the early stages of cancer with low-malignant potential and, therefore, it would appear reasonable to have screening techniques in place for patients presenting with cryptogenic stroke.¹⁶

A number of studies have found that low-molecular-weight heparins, including dalteparin, tinzaparin and semuloparin,⁹ reduce the risk of venous thromboembolism in patients with cancer. It is unclear, however, as to whether these results can be inferred to arterial thrombosis. Previous cases of patients with ovarian cancer found that anticoagulation alone did not completely alleviate the hypercoagulable state found in these patients, with recurrent episodes of venous and arterial thromboembolic events occurring despite adequate anticoagulation.²¹ Studies that have looked at surgical interventions such as curative resection and cytoreductive surgery with anticoagulation and chemotherapy, however, have reported treatment of the hypercoagulability state avoiding recurrent thromboembolic events.^{17 22} More studies are required to determine the optimal management of ischaemic stroke in patients with underlying malignancy.

In summary, we have described a case of young woman presenting with emboli stroke of unknown cause as the first

manifestation of an ovarian carcinoma. Our case highlights the necessity of investigating patients presenting with cryptogenic stroke for underlying malignancy. Investigations such as for D-dimer levels and tumour markers, and breast and testicular examinations, as well as intra-abdominal and pelvic imaging, may result in earlier detection of occult malignancy and better outcomes for these patients.

Learning points

- ▶ Ischaemic strokes in young patients are rare and often a diagnostic challenge.
- ▶ The most common causes of ischaemic strokes in young patients are cerebral vascular abnormalities and cardiac abnormalities.
- ▶ Young patients presenting with ischaemic stroke for which a cause cannot be determined should be screened for an underlying malignancy.
- ▶ Screening tools can include D-dimer levels, tumour markers, breast and testicular examinations, and intra-abdominal and pelvic imaging.
- ▶ The early detection of occult malignancy can result in better outcomes for patients.

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Contributors LMB and DS were involved in the patient's care on the first admission and helped in the writing and analysis of this manuscript. DS helped initiate the manuscript authorship and was involved in the management of deadlines and case write up. LB helped write the discussion and helped with the final conceptualisation and quality of the case.

Competing interests None declared.

Patient consent Obtained.

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