CASE REPORT

Paraneoplastic cerebellar degeneration secondary to ovarian carcinosarcoma: a cerebellar conundrum

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SUMMARY

We present a case of an elderly female patient who presented with a 6-month history of progressive slurred speech, vertigo, unsteadiness and falls. She underwent an extensive battery of neurological and cardiovascular investigations, none of which demonstrated a diagnostic cause for her symptoms. She was referred to the stroke and neurology teams and was started on treatment for presumed anxiety. As her symptoms continued to progress, she was referred to the falls service. Following a multidisciplinary team discussion, she was reviewed by the consultant geriatrician who felt this may be due to a malignancy so the consultant geriatrician arranged blood tests and CT scan of her chest, abdomen and pelvis. These demonstrated a large left adnexal mass and a raised Ca-125 level. The patient was diagnosed with an ovarian tumour, which was treated surgically. A provisional diagnosis of paraneoplastic cerebellar degeneration, secondary to ovarian carcinosarcoma, was made.

BACKGROUND

We report on the diagnostic and therapeutic challenges of this unusual case and its implications for other patients with similar symptoms. Sadly, it took almost 3 years from her initial onset of symptoms to get to the provisional diagnosis of paraneoplastic cerebellar degeneration (PCD), secondary to ovarian cancer. In this time, the patient had deteriorated from complete independence to requiring assistance with care.

CASE PRESENTATION

A 73-year-old Caucasian female presented to her general practitioner with a 6-month history of progressive slurred speech, vertigo, unsteadiness and falls. She also reported a loss of dexterity that was worse with her dominant right hand.

She had a medical history of tuberculosis, hypertension and had previously had carpal tunnel surgery and a left thyroid lumpectomy. She had no psychiatric history and no family history of any psychiatric or neurological disorders. She lived with and cared for her elderly husband who suffered from Alzheimer's disease. She was a non-smoker and non-drinker who was, prior to symptom onset, cognitively intact, fully independent in her activities of daily living and able to drive.

In view of her symptoms, age and history of hypertension, she was referred to the stroke service as a probable minor stroke. A CT scan of her head revealed a small lacunar stroke and an incidental

small meningioma. However, these did not explain her symptoms, and it was felt likely that the main cause of her symptoms were psychological (anxiety secondary to carer burden).

INVESTIGATIONS

The patient had an extensive battery of neurological and cardiovascular investigations. Her blood tests were normal, a tilt table did not reveal a postural drop or provoke symptoms and a Dill-Hall-Pike test was normal. In addition, she also had a carotid Doppler, 24 hours ECG and a transthoracic echocardiogram, which were also normal. Her MRI of the head confirmed the findings of her CT of the head but did not show any new pathology to explain her symptoms.

Following this, she had an in-depth neuropsychological assessment by a consultant neurologist and psychologist, which suggested that anxiety and carer-burden to be the likely cause of her symptoms. A repeat MRI scan of her head showed no new changes, and a lumbar puncture was normal.

Following her assessment at the falls clinic, she had a repeat set of bloods that included tumour markers for screening for underlying occult malignancies. These blood tests revealed a raised Ca-125 level of 1480 U/mL. She had a CT scan of her chest, abdomen and pelvis, which revealed a large left adnexal mass measuring approximately 10 cm × 7 cm. She was diagnosed with FIGO stage IIA carcinosarcoma involving her left fallopian tube and both ovaries, but no distal metastases were seen on imaging.

DIFFERENTIAL DIAGNOSIS

The progressive nature of patient's symptoms meant that stroke was an unlikely diagnosis. Due to the lack of a diagnosis and the patient's advancing symptoms, an underlying occult malignancy was suspected. The screening bloods and CT scan confirmed a diagnosis of ovarian cancer. In view of her clinical symptoms, the diagnosis of an underlying occult malignancy and no other unifying diagnosis, a diagnosis of PCD was made. A lumbar puncture to test for paraneoplastic antibodies was suggested, but the patient declined. Following her review by a geriatrician, she was referred to a neurologist who confirmed PCD secondary to ovarian carcinosarcoma as the likely diagnosis.

TREATMENT

Following discussion at the relevant cancer multidisciplinary meeting, the patient was referred to the surgeons for removal of the tumour. She had

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a laparotomy with bilateral salpingo-oophorectomy, omentectomy and removal of lymph nodes. The postoperative pathology report confirmed a carcinosarcoma arising from the left fallopian tube with no malignant cells found in the lymph nodes, omentum or peritoneum. These samples were not tested for paraneoplastic antibodies. Following the operation, her Ca-125 level reduced from 1480 to 386 U/mL. The patient was offered adjuvant chemotherapy, which she subsequently declined primarily due to concerns about her fitness and the anticipated success of the operation. She was also advised by her oncologist that the chance of a neurological recovery was unlikely to be improved by chemotherapy. Of note, a postoperative CT scan showed no evidence of residual disease. The patient was offered treatment for PCD but declined any further treatment.

OUTCOME AND FOLLOW-UP

Despite the diagnosis and management of the ovarian tumour, the patient continued to deteriorate. She continued to fall and unfortunately sustained a fractured neck of femur that resulted in an operation and a prolonged hospital stay for inpatient rehabilitation. After discharge, she was reviewed regularly with her family in the geriatric outpatient clinic, but her symptoms did not appear to show any signs of improvement. Serial blood tests showed a stable Ca-125 level and no detectable serum paraneoplastic antibodies (anti-Yo, anti-Ri, anti-Hu and anti-Tr). The aim remains to arrange a lumbar puncture to detect paraneoplastic antibodies to confirm the diagnosis. However, in view of her ongoing deterioration and general frailty, the patient declined this procedure and so is unlikely to take place. It was felt that this would not alter management of the individual patient.

DISCUSSION

PCD is a relatively rare syndrome that affects around 1% of cancer patients.¹ While most malignant tumours have been associated with paraneoplastic syndromes,¹ PCD is commonly associated with ovarian, breast or lung cancer (particularly small cell lung cancer) or lymphoma (particularly Hodgkin's).¹² The disease usually affects patients in later life, with a median age of onset between 64 and 67 years of age.¹ In the UK, it appears that paraneoplastic syndromes tend to affect female patients more than their male counterparts at more than 3:1, but this has not been reproduced in studies globally.¹

It is believed that PCD is triggered by an abnormal immune system response to an underlying malignant tumour, due to the sharing of common antigens with nervous tissue.³ Postmortem studies on patients with PCD have shown a significant loss of Purkinje cells and inflammatory infiltrates in the early stages of the disease.² The most common antibodies associated with cerebellar dysfunction are anti-Yo and anti-Tr;¹ anti-Yo antibodies (also called Purkinje cell antibody type 1 or PCA-1) are most commonly found with breast cancer or gynaecological cancers,¹ while anti-Tr antibodies are associated with Hodgkin's disease.¹ However, this remains a challenge as not all biomarkers have commercially available testing and 40% of patients do not have antibodies identified, making this an important area for ongoing research.⁴ With this in mind, Graus *et al* have proposed diagnostic criteria for paraneoplastic syndromes that determines if the diagnosis is 'definite' or 'possible'; in a patient with 'classical' symptoms, antibodies are not required to make a 'definite' diagnosis.⁵

Patients may experience a prodromal viral-like illness prior to the onset of neurological symptoms,² commonly an unsteady gait that then progresses to ataxia, diplopia, dysarthria and

dysphagia.² This process may last for weeks,³ and then progresses towards severe disability.¹⁴ While PCD remains difficult to diagnose, the key is to discover and treat the underlying tumour.¹³ After sending serum and cerebrospinal fluid samples for paraneoplastic biomarkers, screening for tumours should be carried out urgently with some authors advocating the early use of positron emission tomography (PET) scanning as this may show small tumours that may be missed by conventional imaging.¹ Other investigations are useful only to rule out other causes of cerebellar dysfunction, but MRI scans may reveal cerebellar atrophy.⁶

As with our patient, the majority of patients (70%) do not have a cancer diagnosis at the onset of their neurological symptoms,² and up to 20% may never have a confirmed diagnosis of malignancy.¹ Early diagnosis and management of the underlying tumour remains important, as this may provide neurological stabilisation and may even lead to an improvement in symptoms.¹³ Many therapies have been trialled, in particular corticosteroids, plasma exchange, intravenous immunoglobulins (IVIg) and immunosuppressant therapy.² Some success has been found in the use of IVIg, with a review of 15 cases suggesting that IVIg may be of use, particularly if used within 3 months of symptom onset.⁷

As PCD is rare and challenging to diagnose, little is known about survival and prognosis. However, in a review of 50 cases, it was found that anti-Tr antibodies, younger age, less severe disability at diagnosis and prompt treatment of malignancy appear to affect prognosis favourably.⁸ Sadly, most patients will deteriorate and become severely disabled, with 75%–80% of patients becoming non-ambulatory,¹ despite achieving remission from malignancy.^{1–3}

Learning points

- ▶ Consider rare diagnoses when patients do not respond to treatment or have medically unexplained symptoms.
- ▶ Beware of attributing symptoms to stress, anxiety or other mental health conditions without excluding organic causes.
- ▶ Clinicians should consider arranging a wide panel of screening tests in cases such as this, in particular to consider the possibility of an underlying occult malignancy.
- ▶ Paraneoplastic cerebellar degeneration is a rare syndrome that remains difficult to diagnose, and treatment appears unlikely to improve neurological symptoms but often halts progression.
- ▶ If this patient had been diagnosed and treated earlier, her neurological decline may not have been as severe.

Contributors The patient was reviewed in clinic by TV and KR. She was reviewed subsequently by JDB and AS as an inpatient, then subsequently in clinic. The manuscript was written by JDB with input from all authors. All authors have reviewed and altered the manuscript and its subsequent revisions. All authors agreed on the final version prior to submission.

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