CASE REPORT

# Paraneoplastic cerebellar degeneration associated with serous adenocarcinoma of the ovary

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## SUMMARY

We report a case of a 68-year-old woman who presented with symptoms of cerebellar degeneration which initiated a suspicion of underlying malignancy. The patient presented with progressive ataxia and dysarthria and after excluding primary cerebellar pathology, paraneoplastic syndrome was suspected and she was investigated for a malignancy. CT scan of the pelvis showed a left-sided ovarian mass later diagnosed as serous adenocarcinoma of the ovary. She underwent surgery and histology of the mass showed poorly-differentiated serous adenocarcinoma. Paraneoplastic neurological syndrome encompasses several neurological disorders including paraneoplastic cerebellar degeneration (PCD) caused by an immune-mediated mechanism in patients with an underlying malignancy. PCD is a rare condition that occurs in less than 1% of patients with cancer and is associated with specific groups of cancer. It is important to identify PCD due to its association with certain cancers and also to limit the disabilities associated with the syndrome.

## BACKGROUND

Paraneoplastic neurological syndrome is caused by immune-mediated mechanisms in patients with an underlying malignancy and encompasses several neurological disorders including paraneoplastic cerebellar degeneration (PCD). Paraneoplastic neurological syndromes are diagnosed after exclusion of other known causes of neurological symptoms in the presence of cancer. PCD is a rare condition that occurs in less than 1% of patients with cancer and occurs predominantly in patients with cancer of the ovary, uterus, breast, small-cell carcinoma of the lung or Hodgkin's lymphoma.[1–3] It is characterised by subacute cerebellar symptoms of vertigo, dysarthria and cerebellar ataxia. In this paper, we report a case of a 68-year-old woman who presented with symptoms of PCD and was subsequently diagnosed with a poorly differentiated serous adenocarcinoma of the ovary.

## CASE PRESENTATION

A 68-year-old woman presented with a 7-week history of rapidly progressive ataxia, slurred speech and recurrent falls. She was previously well with a medical history of mild asthma. On examination there was evidence of ataxia, dysarthria and right leg weakness. A lumbar puncture was performed which produced blood stained fluid containing lymphocytes and monocytes. However, no organisms or malignant cells were seen. The laboratory parameters of white cell count, red blood cells, protein and glucose in the cerebrospinal fluid were all within the normal range. An MRI of the brain was performed which was completely normal with no evidence of infection, space occupying lesion or malignancy. Owing to the lack of raised inflammatory markers and a negative MRI of the brain, subacute paraneoplastic cerebellar syndrome was considered. *Detection for the presence of antineuronal antibodies in the serum was performed and anti-Yo antibody was found to be positive.*

Bilateral mammograms were carried out which showed no evidence of suspicious masses, distortion or calcification. A CT scan of the thorax, abdomen and pelvis was then performed and this showed a 7×3.5 cm soft tissue mass seen adjacent to the uterus with an associated 13×6 cm fluid density lesion. While there was no evidence of peritoneal disease, an ovarian malignancy could not be excluded. Cancer antigen 125 (CA-125) level was measured and was elevated at 112 (normal parameters are 0–35 kU/L).

Following discussion in the gynaecological multidisciplinary team, she underwent a left-sided salpingo-oopherectomy which was submitted as a frozen section and showed a poorly differentiated serous adenocarcinoma of the ovary. The operation then proceeded to a total hysterectomy and contralateral salpingo-oopherectomy with upper paraaortic, vena caval, right external iliac and left external lymph nodes harvest and omentectomy. Following surgical resection, the patient was started on chemotherapy.

## INVESTIGATIONS

### Histopathology findings

The uterus, cervix, right tube and ovary were of normal macroscopic size and appearance.

The left ovary contained a partially solid and partially cystic ovarian cyst weighing 383 g with a smooth outer surface and measured 132×60×60 mm. On opening it was filled with serous fluid containing some shiny particles. The solid area measured 55×45×35 mm and was tan and lobulated in appearance with focal haemorrhage and necrosis. No macroscopic metastases were evident in the lymph nodes or omentum. Paraffin sections confirmed the frozen section findings of high-grade serous adenocarcinoma of the ovary (figures 1 and 2). The tumour cells were strongly positive for AE1/3, CA-125, estrogen receptor, progesterone receptor (focally) and strongly and diffusely positive for WT1 and P53. The tumour cells were negative for CDX2, thyroid transcription factor 1 and CD45. One of 11 lymph

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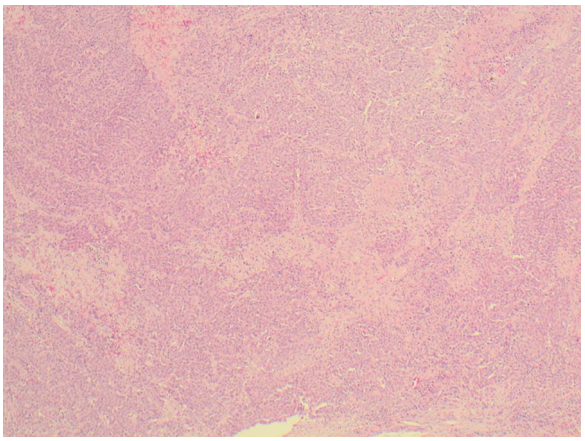

**Figure 1** Poorly-differentiated serous adenocarcinoma of the ovary with abundant necrosis (×4 magnification).

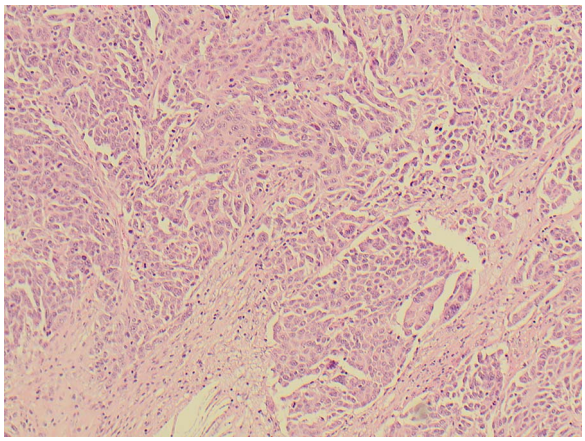

**Figure 2** Poorly-differentiated serous adenocarcinoma of the ovary with abundant necrosis (×10 magnification).

nodes harvested were positive, in the para-aortic region which increased the Federation of Gynecology and Obstetrics staging to 3C. Sections from the cervix showed no evidence of cervical intraepithelial neoplasia, cervical glandular intraepithelial neoplasia or invasive malignancy. The endometrium was inactive with no evidence of chronic endometritis, hyperplasia, atypia or malignancy and the myometrium was unremarkable.

## OUTCOME AND FOLLOW-UP

Following the surgical resection of the tumour, the patient underwent six cycles of chemotherapy over 18 weeks and is left with no evidence of residual disease. During the course of her chemotherapy, she was diagnosed with a lower leg deep vein thrombosis and has been maintained on 12 500 units of Fragmin daily. As is often the case, unfortunately the cerebellar damage was not reversed by the cancer treatment and she was left with a level of disability, which she is working extremely hard with physiotherapy and speech therapy to try and improve. Her mobility and speech have continued to slowly improve and further improvements are expected. However, a residual level of disability is expected, the extent of which cannot be estimated.

## DISCUSSION

Although it is estimated that less than 15% of malignancies develop an associated paraneoplastic syndrome,[4] recognition of the clinical manifestations of the syndrome remains vital as the symptoms can precede those of the underlying malignancy, sometimes by months or even years, as PCD is sometimes secondary to very small malignant tumours that are barely detectable by CT or MRI.[5 6]

PCD is characterised by degeneration of cerebellar Purkinje neurons[7 8] and several antineuronal antibodies are implicated in this degeneration, including Yo, Hu, Ri and Ma.[9] Anti-Yo antibody, in particular, has been linked with ovarian and breast cancers associated with PCD.[10] Studies have shown that 88% of patients with paraneoplastic cerebellar degeneration express high titres of anti-Yo.[11] Our patient's positive anti-Yo antibody is in keeping with this study. However, it is interesting to note that 20% of patients with ovarian cancer without neurological symptoms also express Yo antigens in their tumours.[12]

Although the detection of antineuronal antibodies is not necessary to establish a diagnosis of PCD, their presence do aid in the diagnosis, particularly when the underlying malignancy is not located. Cases have been reported where cerebellar degeneration has preceded the tumour by as long as 5 years after expression of the anti-Yo antibody.[13] However, if the diagnosis of paraneoplastic syndrome has been established and the source of malignancy identified, serum antibodies are of limited benefit. Fluctuations in clinical symptoms do not reflect the measured levels of serum antineuronal antibody.[14] Also, antibody levels may remain elevated for several years after the treatment of the underlying malignancy[14] therefore they cannot be used to assess response to treatment.

Any detection of signs of cerebellar dysfunction in a patient should elicit urgent investigations such as routine bloods, assessment of cerebrospinal fluid and imaging such as MRI of the brain. If cerebellar pathology such as infection, space occupying lesion or demyelination is ruled out, then paraneoplastic syndrome must be suspected and extra investigations arranged to locate the source of malignancy. MRI of a PCD brain without any coexisting aetiology would not show any changes however if the PCD is in advanced stage, the scan may show cerebellar atrophy.

The imaging investigations performed following a presentation of PCD are based on the site of malignancies most commonly associated with paraneoplastic syndrome and include mammograms and CT scans of thorax, abdomen and pelvis. Positron emission tomography scans are usually reserved to identify smaller focal carcinomas not otherwise detected by other imaging modalities. The use of whole body scans also serves to assess for the presence of metastases which may affect prognosis and subsequent management of the patient's condition. Other investigations can include chest X-rays, ultrasound and endoscopies. In the event that no malignancy is identified and other causes are excluded, follow-up interval imaging at 6–12 months should be considered.[15]

As particular cancers are associated with particular tumour markers, tumour markers may be utilised to indicate or narrow down the possible sites of tumour or to aid a malignant suspicion of an abnormal mass. However, due to poor specificity, clinical decisions cannot be made based on abnormal tumour markers alone. With regards to CA-125, a tumour marker associated with ovarian tumours, abnormal elevation in asymptomatic postmenopausal women has been associated with a 36-fold increase in risk of ovarian cancer.[16] In our case, the patient's elevated CA-125 supported the clinical suspicion of ovarian malignancy but tissue diagnosis was obtained through a frozen section to verify the diagnosis prior to proceeding to major resection and lymph node harvesting.

The cerebellar syndrome may be severe enough to affect the patient's ability to conduct activities of daily living independently, affecting their overall quality of life. Though there have been attempts to treat the neurological symptoms using chemotherapy, immunosuppression and/or immunoglobulins, no significant improvement in patient's clinical symptoms were yielded.[17] The main determinant of overall survival is the surgical resection of the neoplasm in conjunction with chemotherapy. Although tumour resection has been associated with stabilisation and rarely, complete cessation of neurological symptoms, only mild-to-moderate neurological improvement has been associated with ovarian patients with cancer with PCD.[18] Intensive rehabilitation therefore plays a vital role in regaining functional recovery and may encompass speech therapy and counselling.[19] Antibodies may persist indefinitely even following the cure of the underlying malignancy.[20] Early detection of PCD may lead to early localisation and management of a malignancy, thereby limiting the ensuing neurological disability associated with this condition while improving the overall survival of the patient.

## Learning points

- Paraneoplastic cerebellar degeneration (PCD) is a rare condition that occurs in less than 1% of patients with cancer and occurs predominantly in patients with cancer of the ovary, uterus, breast, small-cell carcinoma of the lung or Hodgkin's lymphoma.[1–3]
- PCD is characterised by subacute cerebellar symptoms of vertigo, dysarthria and cerebellar ataxia and develops following degeneration of cerebellar Purkinje neurons.[7 8] Several antineuronal antibodies are implicated in this degeneration.
- Although less than 15% of malignancies develop an associated paraneoplastic syndrome,[4] recognition of the clinical manifestations of the syndrome remains vital as the symptoms can precede those of the underlying malignancy, sometimes by months or even years.
- Early detection of PCD may lead to early localisation and management of a malignancy thereby limiting the ensuing neurological disability associated with this condition while improving the overall survival of the patient.

**Contributors** LG was involved in conception, design and final approval of the version published. DBS took part in acquisition of the data, drafting the article and revising it critically for important intellectual content.

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**Patient consent** Obtained.

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