CASE REPORT

Paraneoplastic cerebellar degeneration with bilateral facial palsy: a rare primary presentation of breast cancer

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SUMMARY

Paraneoplastic cerebellar degeneration is a rare dysfunction of the cerebellum associated with malignancy. Nevertheless, it is the most common paraneoplastic syndrome affecting the brain. A 50-year-old woman presented to the neurology outpatient department (OPD) with symptoms of cerebellar dysfunction since 4 months and complaints of a painless lump in the right breast and drooling from mouth since 1 month. Examination revealed classical signs of cerebellar dysfunction and a 5×5 cm lump in the right breast with a single right axillary lymph node. Serum anti-Yo antibody titre was strongly positive. The patient was referred to General Surgery OPD for opinion. After establishing the diagnosis of right breast carcinoma; she underwent a right modified radical mastectomy. She was referred to the oncologist for chemo/radiotherapy but because of poor performance status, only symptomatic treatment was pursued. Follow-up till now shows no improvement in the neurological dysfunction.

spoken with varying force and noticeable pauses. There was also a complaint of a painless lump in the right breast of size 5×5 cm for past 1 month. She was postmenopausal with no significant personal, family and medical history.

General examination revealed stable pulse rate and blood pressure with a Karnofsky performance score of 50. Neurological examination revealed truncal and limb ataxia, bilateral symmetrical dysidiadochokinesia, dysmetria, intentional tremors with impaired finger nose finger and heel shin test and bilateral facial palsy (figure 1). There was a 5×5 cm lump in right breast with 2×2 cm palpable right axillary lymph node. Gynaecological and other

BACKGROUND

Paraneoplastic cerebellar degeneration (PCD) is a non-metastatic neurological dysfunction that occurs as a result of production of antitumour antibodies which cross-react with the normal tissue antigens in the cerebellum. It is the most common paraneoplastic syndrome affecting the brain.¹ However, this occurs only in less than 1% of patients with cancer.² According to a report published in 2013, fewer than 250 cases of PCD have been reported in the literature.³ It is characterised by severe cerebellar dysfunction, typically beginning with gait ataxia and progressing, over weeks to months, to severe symmetrical truncal and limb ataxia. Pathologically, there is extensive Purkinje cell loss occasionally associated with meningeal and deep cerebellar nuclear inflammatory infiltrates.^{4–6} PCD with bilateral facial palsy is a rare primary presentation of carcinoma breast.

CASE PRESENTATION

A 50-year-old woman presented to the neurology OPD with chief complaints of unsteadiness while walking, intentional tremors in both hands for past 4 months, slurring of speech for past 2 months and drooling of saliva from bilateral angles of mouth for past 1 month. The speech, according to the patient's relatives, was comprehensible but

Figure 1 Patient's face showing bilateral facial nerve palsy.

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Figure 2 MRI brain (sagittal section upper two rows and axial section last row) showing normal cerebellum.

systemic examination was normal. History and examination revealed no cognitive deficits or any affective disorder.

INVESTIGATIONS

MRI brain was normal with minimal prominence of bilateral cerebellar folias (figure 2). Serum anti-Purkinje cell ABS (anti-Yo) antibody titre was strongly positive. Serum antineuronal nuclear antibody 1 (anti-Hu), anti-Ri antibodies, Paraneoplastic antigen Ma2 (PNMA2) antibodies and amphiphysin antibodies were negative. Cerebrospinal fluid (CSF) analysis for anti-Yo antibody levels, total protein levels and white cell count is an essential investigation for supporting the diagnosis. Our patient did not consent for a lumbar puncture because of which CSF analysis could not be done. Fine needle aspiration cytology (FNAC) from the right breast lump was reported as 'ductal carcinoma'. Based on clinical examination findings and investigations, a provisional diagnosis of PCD due to breast cancer was suspected. For further management, the patient was referred to the general surgery department.

Core needle biopsy of the breast lump showed infiltrating ductal carcinoma; negative for oestrogen and progesterone receptors and positive for human epidermal growth factor receptor 2. FNAC of axillary lymph node showed tumour deposits. Complete blood counts, liver function and renal function tests were essentially normal. Chest radiograph was suggestive of no metastatic lesions or pleural effusion. Bilateral mammography

reported a Breast Imaging Reporting and Data System (BIRADS) 6 for right breast and a BIRADS 1 for the left breast. Ultrasonography scan of the abdomen and pelvis was normal. Technetium 99m bone scintigraphy revealed no bony metastasis.

DIFFERENTIAL DIAGNOSIS

Diseases or conditions which may present with similar signs and symptoms with an underlying malignancy include the following.

1. Cerebellar metastasis.
2. Chemotherapy toxicity.

Diseases which may present with cerebellar dysfunction without an associated malignancy include.

1. Infectious cerebellitis.
2. Miller Fisher syndrome.
3. Anti-glutamic acid decarboxylase (GAD) antibody associated cerebellar ataxia.
4. Gliadin-associated cerebellar ataxia.
5. Creutzfeldt-Jacob disease.
6. Alcohol related, vitamin B or E deficiency and toxin-related cerebellar ataxia.

TREATMENT

A diagnosis of early invasive right breast carcinoma (T2N1M0, Stage IIB)⁷ was made after thorough evaluation. The patient underwent right modified radical mastectomy (MRM) with an

Figure 3 Histopathology microphotograph. H&E 40 $\times$. Atypical cells arranged in acini and clusters with frequent mitosis consistent with infiltrating ductal carcinoma.

uneventful postoperative recovery period. Histopathology of the resected specimen showed infiltrating ductal carcinoma with negative margins (figure 3), extensive lymphovascular invasion and 8 out of 18 lymph nodes were positive for malignancy. Thereafter, the patient was referred to the medical oncology department at our institute, for evaluation and feasibility of chemotherapy/radiotherapy. However, considering the poor Karnofsky performance score (50) of the patient, the decision to administer adjuvant chemotherapy or radiotherapy was deferred and only symptomatic treatment was offered.

OUTCOME AND FOLLOW-UP

The patient continued to follow-up, in person, in the surgery OPD till 2 months after MRM. After suture removal, she was referred to the neurology OPD for evaluation of the neurological status. The patient, however, did not follow-up there. Thereafter, the health of the patient was inquired after from the patient's son telephonically, on monthly intervals. The patient did not receive any specific treatment for the neurological condition. Postoperative serum levels of anti-Yo antibody could not be estimated as the patient did not follow-up in Neurology OPD. After 6 months of surgery, there has been no improvement in her neurological dysfunction. Nevertheless, there is no further deterioration and her condition remained stable. However, she still requires assistance for self-care and the quality of life is still poor.

DISCUSSION

PCD is an array of neurological disorders resulting from tumour-induced autoimmunity against cerebellar antigens.⁸ There are nearly 30 different antibodies associated with this condition and the most common is anti-Yo or anti-Purkinje cell cytoplasmic antibody-1 (PCA-1), which accounts for nearly 50% of cases.⁹ After studying 50 patients with antibody associated PCD, the researchers found that 19 patients had anti-Yo, 16 anti-Hu, seven anti-Tr, six anti-Ri and two anti-mGluR1 antibodies. It was observed that all of the patients with anti-Yo, anti-Tr and anti-mGluR1 antibodies suffered from PCD. In 84% of the patients, a tumour was identified and the most common associated with anti-Yo antibody were gynaecological and breast cancers.⁸ More

than 200 cases of PCD have been described in the literature, but PCA-1 antibodies are almost exclusively seen in carcinomas of the ovary, uterus and breast in women.¹⁰ PCA-1 is not responsible for the cerebellar degeneration since its target antigen; human cerebellar degeneration-related protein-2 (Cdr2) is intracellular and therefore not accessible to the antibodies.^{11 12} Cdr2 is usually present in the cytoplasm of brainstem neurons and Purkinje cells^{13–15} but is abnormally expressed in about 62% of ovarian tumours.¹⁶ A possible mechanism leading to cerebellar degeneration is the cytotoxic T lymphocytes (CTLs) mediated attack on the neural cells, which is supported by the presence of CTLs in the bloodstream and CSF of patients with PCA-1 positive PCD.¹⁷ Majority (89%) of the patients with PCA-1 positive PCD presented with cerebellar ataxia; 23% of the patients had other neurological problems and 11% suffered from non-cerebellar disorders.¹² Patients have also presented with brainstem disorders, myelopathy,^{8 10} peripheral neuropathy,^{10 18} motor neuropathy,¹⁹ gastrointestinal dysmotility,²⁰ downbeat nystagmus,²¹ chorea²² and cognitive impairment.¹⁰ The distribution of cdr2 in the neocortical and brainstem neurons and the cerebellum²³ forms the pathological basis for the extracerebellar array of signs and symptoms the affected patients exhibit. Histopathological examination of the neural tissue after autopsy of two patients who died of this disease showed multifocal inflammatory changes associated with parenchymal and perivascular CD8⁺ cytotoxic T lymphocytes present in the cerebellum, brainstem, spinal cord and nerve rootlets.¹² The patient described in this report presented with facial diplegia or bilateral facial nerve palsy along with signs and symptoms of PCD. Bilateral facial nerve palsy can probably be attributed to the autoimmune response (CD8⁺ cytotoxic T lymphocytes) mounted by the body against the cdr2 protein present in the brainstem, as described previously. Patients with PCA-1 autoimmunity have a far worse neurological prognosis than patients with PCD who test positive for other antibody types.^{12 24}

Classical subacute cerebellar degeneration is defined by the following criteria: severe pancerebellar syndrome which has developed in less than 12 weeks, with no evidence of cerebellar atrophy (except from that due to senile changes) on MRI and a RANKIN score of at least three (symptoms prevent totally independent existence). Paraneoplastic syndromes are diagnosed by two criteria: definite and possible.

The definite peripheral nervous system (PNS) criteria consists of the following.

1. A classical syndrome associated with a cancer which develops within 5 years of the neurological dysfunction.
2. A non-classical syndrome, which resolves with cancer treatment without any immunotherapy. The syndrome is not otherwise known to improve spontaneously.
3. A non-classical syndrome associated with onconeural antibodies and a cancer developing within 5 years of onset of neurological disorder.
4. A neurological syndrome with fully characterised onconeural antibodies (anti-Hu, Yo, Ri, Ma2, amphiphysin) without any cancer.

The possible PNS criteria consists of:

1. A classical syndrome with no cancer or onconeural antibodies, but having a significant risk of tumour.
2. A neurological syndrome with partially characterised onconeural antibodies but no cancer.
3. A non-classical syndrome, no onconeural antibodies and cancer occurring within 2 years of diagnosis.²⁵

Patients with PCD usually succumb to death due to the progression of the underlying tumour rather than the neurological

Learning points

- ▶ Subacute cerebellar degeneration or paraneoplastic cerebellar degeneration (PCD) with bilateral facial nerve palsy is a rare presentation of carcinoma breast.
- ▶ A patient presenting with cerebellar dysfunction with a normal MRI brain ought to be thoroughly examined and investigated for any underlying malignancy.
- ▶ PCD still remains a difficult condition to treat and is often resistant to therapy.
- ▶ Treatment consists of complete surgical resection (if feasible) of the underlying tumour, immunosuppressive therapy and intense neurorehabilitation.
- ▶ Purkinje cell cytoplasmic antibody type 1 (PCA-1) or anti-Yo autoantibody positivity is associated with a poor prognosis. However, a certain group of patients with PCA-1 PCD have shown improvement after treatment, and hence a trial of therapies is justified.

dysfunction; unless cerebellar degeneration results in dysphagia and aspiration pneumonitis.²⁶ However, an analysis and study of 50 patients with PCD with antineuronal antibodies suggested that almost two-third of the patients having anti-Yo antibody died due to neurological degeneration.⁸ Due to the dearth of prospective studies in the literature as a result of the rarity of the disease; no standard management protocol exists.^{27,28} The treatment of PCD is usually started on empirical basis and should be customised for each patient.²⁷ The primary treatment includes surgical resection of the underlying tumour. This has shown to extend the overall median survival rates. Immunosuppressive therapy in the form of intravenous immunoglobulins along with plasmapheresis, cyclophosphamide or corticosteroids (like methylprednisolone) may be required in the management of the patient.^{29–32} Patients may also require neurorehabilitation, in the form of swallowing and speech therapy.³³ Autologous stem cell transplantation, if available, can be considered as a therapy in a select set of patients who present with a very aggressive progression of PCD.⁸ Despite treatment of the primary tumour and chemotherapy, the prognosis of anti-Yo PCD is rather dismal as there is rarely an improvement in patients' neurological dysfunction.^{34,35} This is due to the fact that by the time treatment is initiated, permanent damage to the Purkinje cell and neurons has already taken place.¹⁰ Unfortunately, the neurological syndrome often handicaps the patient and continues to adversely affect their quality of life much more than the underlying disease.³⁶

In an extensive research involving 133 138 patients, studied over a time period of 21 years, only 83 patients (0.06%) were found to have PCA-1 autoantibody. Out of these 83 patients, cranial neuropathies were observed in 11 patients, where only one patient had bilateral seventh nerve palsy.¹² The rarity of the presentation of signs and symptoms of paraneoplastic cerebellar degeneration with bilateral facial nerve palsy is thus highlighted in this case report.

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REFERENCES

- 1 Liu S, Tunkel R, Lachmann E, et al. Paraneoplastic cerebellar degeneration as the first evidence of cancer: a case report. *Arch Phys Med Rehabil* 2000;81:834–6.
- 2 Braik T, Evans AT, Telfer M, et al. Paraneoplastic neurological syndromes: unusual presentations of cancer. A practical review. *Am J Med Sci* 2010;340:301–8.
- 3 McHugh JC, Tubridy N, Collins CD, et al. Unusual MRI abnormalities in anti-Yo positive "pure" paraneoplastic cerebellar degeneration. *J Neurol* 2008;255:138–9.
- 4 Brain WR, Daniel PM, Greenfield JG. Subacute cortical cerebellar degeneration and its relation to carcinoma. *J Neurol Neurosurg Psychiatry* 1951;14:59–75.
- 5 Brain L, Wilkinson M. Subacute cerebellar degeneration associated with neoplasms. *Brain* 1965;88:465–78.
- 6 : Henson RA, Urich H, eds. *Cancer and the nervous system: the neurological manifestations of systemic disease*. Oxford, UK: Blackwell Scientific, 1982:346–67.
- 7 Brunicardi FA, Anderson DK, Billiar TR, et al. *Schwartz principles of surgery*. 10th edn. New York: McGraw-Hill Education, 2015:532–4.
- 8 Shams'ili S, Grekens J, de Leeuw B, et al. Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. *Brain* 2003;126:1409–18.
- 9 Hammack JE, Kimmel DW, O'Neill BP, et al. Paraneoplastic cerebellar degeneration: a clinical comparison of patients with and without Purkinje cell cytoplasmic antibodies. *Mayo Clin Proc* 1990;65:1423–31.
- 10 Peterson K, Rosenblum MK, Kotanides H, et al. A clinical analysis of 55 anti-Yo antibody-positive patients. *Neurology* 1992;42–.
- 11 Tanaka K, Tanaka M, Igarashi S, et al. Trial to establish an animal model of paraneoplastic cerebellar degeneration with anti-Yo antibody. 2. Passive transfer of murine mononuclear cells activated with recombinant Yo protein to paraneoplastic cerebellar degeneration lymphocytes in severe combined immunodeficiency mice. *Clin Neurol Neurosurg* 1995;97:101–5.
- 12 McKeon A, Tracy JA, Pittock SJ, et al. Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. *Arch Neurol* 2011;68:1282–9.
- 13 Okano HJ, Park WY, Corradi JP, et al. The cytoplasmic purkinje onconeural antigen cdr2 down-regulates c-Myc function: implications for neuronal and tumor cell survival. *Genes Dev* 1999;13:2087–97.
- 14 Rodriguez M, Truh LI, O'Neill BP, et al. Autoimmune paraneoplastic cerebellar degeneration: ultrastructural localization of antibody-binding sites in Purkinje cells. *Neurology* 1988;38:1380–6.
- 15 Greenlee JE, Brashear HR. Antibodies to cerebellar Purkinje cells in patients with paraneoplastic cerebellar degeneration and ovarian carcinoma. *Ann Neurol* 1983;14:609–13.
- 16 Totland C, Aarskog N, Eichler T, et al. CDR2 antigen and Yo antibodies. *Cancer immunology. Immunotherapy* 2011;60:283–9.
- 17 Albert ML, Darnell JC, Bender A, et al. Tumor-specific killer cells in paraneoplastic cerebellar degeneration. *Nat Med* 1998;4:1321–4.
- 18 Konanc D, O'Neill BP, Caselli RJ, et al. Peripheral neuropathic presentation in 3 patients with seropositivity for type 1 anti-Purkinje cell antibodies (PCA-1) and ovarian or related Mullerian carcinoma. *Neurology* 1995;45:A320.
- 19 Khwaja S, Sripathi N, Ahmad BK, et al. Paraneoplastic motor neuron disease with type 1 Purkinje cell antibodies. *Muscle Nerve* 1998;21:943–5.
- 20 Lee HR, Lennon VA, Camilleri M, et al. Paraneoplastic gastrointestinal motor dysfunction: clinical and laboratory characteristics. *Am J Gastroenterol* 2001;96:373–9.
- 21 Cohen AB, Zupa-Fernandez A, Dalmau J, et al. Unusual neuro-ophthalmologic findings in a patient with anti-Yo-associated cerebellar degeneration. *J Neurol Sci* 2004;225(1–2):153–5.
- 22 Krolak-Salmon P, Androdias G, Meyronet D, et al. Slow evolution of cerebellar degeneration and chorea in a man with anti-Yo antibodies. *Eur J Neurol* 2006;13:307–8.
- 23 Corradi JP, Yang C, Darnell JC, et al. A post-transcriptional regulatory mechanism restricts expression of the paraneoplastic cerebellar degeneration antigen cdr2 to immune privileged tissues. *J Neurosci* 1997;17:1406–15.
- 24 Giometto B, Grisold W, Vitaliani R, et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. *Arch Neurol* 2010;67:330–5.
- 25 Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135–40.
- 26 Darnell RB, Posner JB. *Paraneoplastic syndromes, contemporary neurology series*. New York: Oxford University Press, 2011.
- 27 Fanous I, Dillon P. Paraneoplastic neurological complications of breast cancer. *Exp Hematol Oncol* 2015;5:29.
- 28 Ogita S, Llaguna OH, Feldman SM, et al. Paraneoplastic cerebellar degeneration with anti-Yo antibody in a patient with HER2/neu overexpressing breast cancer: a case report with a current literature review. *Breast J* 2008;14:382–4.

- 29 Rupasinghe J, Butler E. Progressive ataxic gait disorder. *J Clin Neurosci* 2007;14:153–7.
- 30 Dorn C, Knobloch C, Kupka M, *et al.* Paraneoplastic neurological syndrome: patient with anti-Yo antibody and breast cancer: a case report. *Arch Gynecol Obstet* 2003;269:62–5.
- 31 Keime-Guibert F, Graus F, Fleury A, *et al.* Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (Anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. *J Neurol Neurosurg Psychiatry* 2000;68:479–82.
- 32 Widdess-Walsh P, *et al.* Response to intravenous immunoglobulin in anti-Yo associated paraneoplastic cerebellar degeneration: case report and review of the literature. *J Neurooncol* 2003;63:187–90.
- 33 Vedeler CA, Antoine JC, Giometto B, *et al.* Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. *Eur J Neurol* 2006;13:682–90.
- 34 Rojas I, Graus F, Keime-Guibert F, *et al.* Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. *Neurology* 2000;55:713–5.
- 35 Widdess-Walsh P, Tavee JO, Schuele S, *et al.* Response to intravenous immunoglobulin in anti-Yo associated paraneoplastic cerebellar degeneration: case report and review of the literature. *J Neurooncol* 2003;63:187–90.
- 36 Peltola J, Hietaharju A, Rantala I, *et al.* A reversible neuronal antibody (anti-Tr) associated paraneoplastic cerebellar degeneration in Hodgkin's disease. *Acta Neurol Scand* 1998;98:360–3.

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