Unusual association of diseases/symptoms

Lhermitte-Duclos and Cowden diseases: breast cancer as an unusual initial presentation of these overlapping conditions

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The authors report the case of a woman presenting with breast cancer who subsequently developed neck pain and ataxia. She had a family history of breast cancer and Cowden disease. A MRI study of the brain revealed a lesion in the cerebellum consistent with Lhermitte-Duclos disease (LDD) and a lesion consistent with a meningioma in the temporal lobe. This case emphasises the importance of awareness of the overlap between LDD and Cowden disease.

BACKGROUND

Lhermitte-Duclos disease (LDD) or dysplastic gangliocytoma of the cerebellum is a rare, slowly progressive unilateral tumour¹ that can cause mass effects in the posterior

fossa. It can be familial or occur sporadically. The characteristic lesions may be present for many years without causing the classic symptoms of headaches, gait ataxia and those of lower cranial nerve involvement.² Pathologically,

Figure 1 Fluid attenuated inversion recovery image shows area of laminated high signal in left cerebellar hemisphere with mass effect.

Figure 2 T2-weighted MRI demonstrates area of variable high signal in left cerebellar hemisphere.

it demonstrates diffuse hypertrophy, chiefly of the stratum granulosum of the cerebellum, with replacement of the granular cell layer and Purkinje cells of the cerebellum.¹ The typical features on standard T1-/T2-weighted MRI (appearance of thickened cerebellar folia giving a laminated or striated appearance) allow a diagnosis without surgery in most cases. Timing of surgical treatment and extent of resection in patients with LDD is unclear. The typical lesions of this disease are usually not clearly demarcated from normal brain tissue and total surgical resection is not always possible.³ Other cerebral abnormalities, especially meningioma⁴ and vascular malformations,⁴ have also been described in LDD.

LDD may occur sporadically or in association with Cowden syndrome (CS), also known as multiple hamartoma neoplasia syndrome. CS is an autosomal dominant inherited cancer syndrome, with age related penetrance, characterised by multiple hamartomas and benign and malignant disease of ectodermal, mesodermal and endodermal origin.³ Affected patients have an increased risk of breast, thyroid and endometrial malignancies, in particular.⁵ The lifetime risk for breast cancer in CS is of the order of 25–50% with the average age of diagnosis made between 38 and 46 years.^{6,7} Pathognomonic features include trichilemmomas, acral keratoses, papillomatous papules and mucosal lesions, with over 80% of patients with CS

exhibiting at least one of these.⁷ Over 80% of patients with CS carry germline mutations of the phosphatase and tensin homolog (PTEN) gene on chromosome 10. Loss of function of PTEN results in constitutive activation of AKT and downstream effectors and correlates with many human cancers, as well as various brain disorders, including macrocephaly, seizures, LDD and autism.

We report the case of a 35-year-old woman who was diagnosed with breast cancer and had a family history of same. She complained of some balance problems and subsequently, a history of Cowden disease was established when the full family history came to light. Imaging of her brain revealed the classic lesion of LDD, and in addition, an incidental meningioma was revealed. The importance of awareness of overlap syndromes in people with cancer is highlighted. The case emphasises the importance of awareness of the overlap between these specific syndromes and the need for rigorous multi-disciplinary follow-up of patients and family members.

CASE PRESENTATION

A 34-year-old woman presented with a suspicious breast lump. She had a medical history of thyroidectomy for benign thyroid disease. This lady had significant family history. Her mother was diagnosed with breast cancer at the age of 57. She also has a maternal aunt with cancer of

Figure 3 T1-weighted image shows area of low signal in left temporal lobe.

unknown origin. One of her four children, aged 4 years, presented with multiple lipomatosis. Three years later, he presented with features suggestive of autism and he was eventually diagnosed by a consensus of a psychiatrist, a neurologist and a geneticist as having CS. Her other son (now aged 13) also tested positively, genetically, for this condition. She underwent genetic testing and was found to be heterozygous for 4bp deletion and 2bp insertion c.698_701delGACGinsAA in exon 7 of the PTEN gene. This is typical of CS. Her other two younger children have not been tested and neither have her parents nor brother.

INVESTIGATIONS

Core biopsy, mammogram and breast ultrasound were performed and she was subsequently diagnosed with multifocal breast carcinoma for which she underwent right-sided mastectomy. Histology revealed a T2N0, oestrogen receptor positive, HER2 negative invasive ductal carcinoma. A bone scan was carried out in order to stage her disease, which revealed focal increased uptake, affecting the left sphenoid bone. Abdominal ultrasound showed two echogenic liver lesions, which were then diagnosed as haemangiomas on CT scan.

Postoperatively, she developed neck pain and ataxia. Neurology consultation was arranged. On examination,

she was of short stature and had kyphoscoliosis. She had moderate nystagmus on lateral gaze and was mildly ataxic on heel-toe walking. She had no other abnormal neurological signs.

As she had a port implant following breast reconstruction surgery she was initially unable to have an MRI of her brain or cervical cord so a CT brain study was performed. This revealed a very swollen posterior fossa, suggestive of a cerebellar hamartoma. There was a further lesion in the left temporal lobe with sclerosis of the adjacent sphenoid bone.

She later was able to have an MRI brain study that revealed two lesions- one in the cerebellum with classical features of LDD (figures 1 and 2) and a further lesion consistent with a meningioma in the temporal lobe (figures 3 and 4).

OUTCOME AND FOLLOW-UP

She was reviewed by a dermatologist and was found not to exhibit any cutaneous manifestations of Cowden disease. The brain scans were reviewed by neurosurgery who felt surgery would not be appropriate unless the meningioma was to change in size, as it was not impinging on any vital arteries or nerves.

She is currently receiving tamoxifen and is scheduled to undergo left prophylactic mastectomy.

Figure 4 Post contrast T1-weighted image reveals diffuse enhancement of the temporal lobe lesion most in keeping with an incidental meningioma.

DISCUSSION

In 1981, Russel Jones *et al*⁶ described a previously unreported coincidence of LDD and CD. Since then there have been many similar reports, but the nature of the association between these two diseases remains unclear and the frequency of LDD in patients with CD is unknown. Lok *et al*⁴ performed brain MRI on 20 patients with CD and found that three had radiological features of LDD. In a large series of 31 cases of LDD,⁹ prominent vascular proliferation and vacuolisation of the white matter in many of the lesions was observed. Four patients met the diagnostic criteria for CD and many of the remaining patients had some clinical features of CD. The authors recommended genetic testing and screening for CD in patients with LDD.

Over 80 mutations in the PTEN gene have been reported in Cowden disease.³ It remains unclear whether all cases of LDD, even without features of CS, are caused by germline PTEN mutation and whether somatic PTEN mutation occurs in sporadic LDD. Zhou *et al*,¹⁰ examined a series of 18 patients with LDD, and found that 83% had a PTEN mutation, irrespective of whether they exhibited features of CS. The authors suggested, therefore that the adult-onset LDD be considered a new pathognomic feature of Cowden disease.

The mammalian target of rapamycin (mTOR) is a highly conserved serine/threonine protein kinase that regulates a number of diverse biologic processes important for cell growth and proliferation.⁵ Hyperactivation of the mTOR signalling pathway has been detected in numerous human cancers, including a number of inherited cancer syndromes like LDD. The immunosuppressant rapamycin directly inhibits mTOR activity and a number of its derivatives have been developed as anticancer therapies.¹¹ An immunohistochemical analysis of 18 paraffin embedded LDD lesions¹⁰ indicated activation of the PTEN/AKT/mTOR pathway, suggesting a central role for mTOR in the pathogenesis of LDD. Squarize *et al*¹² reported that the epithelial-specific deletion of PTEN in mice caused the cutaneous lesions typically seen in Cowdens disease and that inhibition of mTOR with rapamycin caused rapid regression of these mucocutaneous lesions. The proven effect of mTOR inhibition on PTEN mutated animal models may prompt investigators to consider these drugs in the prevention of malignancy in patients with Cowden disease, thus giving these patients a treatment option beyond surveillance and preventive surgery.

Learning points

- Breast cancer may be the initial presentation of patients with Cowdens disease.
- There is significant overlap between Cowden disease and Lhermitte-Duclos disease.
- Recognition of this association has direct clinical relevance, because diligent long-term follow-up monitoring of individuals with LDD and CD may lead to the early detection of malignancy.

Competing interests None.

Patient consent Obtained.

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