ELECTRONIC LETTER

Arteriovenous malformations in Cowden syndrome

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Cowden syndrome (OMIM No 158350) is a pleomorphic, autosomal dominant syndrome characterised by hamartomas in tissues derived from the endoderm, mesoderm, and ectoderm. It is caused by germline mutations in the *PTEN* gene and is allelic to the Bannayan–Riley–Ruvalcaba and Lhermitte–Duclos syndromes. The three syndromes are defined on clinical grounds but there is overlap in their definitions. The clinical features include trichilemmomas, verrucose lesions of the skin, macrocephaly, intellectual disability, cerebellar gangliocytoma, thyroid adenomas, fibroadenomas of the breast, and hamartomatous colonic polyps. Cutaneous haemangiomas are occasionally noted. Malignancies often arise in the affected tissues. Visceral arteriovenous malformations are a recognised component of the Bannayan–Riley–Ruvalcaba syndrome but have been reported rarely in Cowden syndrome. A family is described with a clinical diagnosis of Cowden syndrome, a familial frameshift mutation in the *PTEN* gene, and large visceral arteriovenous malformations. The association of these pleomorphic syndromes with arteriovenous malformations can be explained by the putative role of the *PTEN* gene in suppressing angiogenesis. Recognition of arteriovenous malformations as a clinical feature of Cowden syndrome has implications for the clinical management of patients with this disorder.

Cowden syndrome (OMIM No 158350)[1] is an autosomal dominant syndrome characterised by multiple hamartomas of the skin, mucous membranes, brain, breast, thyroid, and colon. In some tissues, the hamartomas are associated with an increased risk of malignancy. The condition was first delineated in 1963[2] and causative mutations have been identified in *PTEN*, a tumour suppressor gene located at 10q23.[3]

The pleomorphic features of Cowden syndrome overlap with some of the features of the Bannayan–Riley–Ruvalcaba syndrome (OMIM No 153480) and Lhermitte–Duclos syndrome (OMIM No 158350). These conditions have been shown to be allelic to Cowden syndrome but had been differentiated on the basis of the patterns of clinical features.

Cutaneous haemangiomas are recognised as occasional features of Cowden syndrome, but visceral arteriovenous malformations (AVM) have rarely been reported. We present two sisters with pathognomonic clinical features of Cowden syndrome, a frameshift *PTEN* mutation, and large visceral AVMs. Two other relatives at risk of having the same *PTEN* mutation also had AVMs.

The association of AVM with mutations of the *PTEN* gene is consistent with the role of the *PTEN* gene in regulating angiogenesis. This association is of clinical significance in the long term management of patients with Cowden syndrome.

CASE REPORTS

Case 1 (GF11097-18)

This woman had multiple facial trichilemmomas, a subcutaneous papilloma, acral hyperkeratoses, a squamous cell carcinoma, and a clear cell acanthoma. The diagnosis of Cowden syndrome was made on dermatological grounds. She was subsequently noted to have macrocephaly (head circumference >98th centile), intraoral papules, and an endometrial polyp. Thus this woman had four pathognomonic features and one major feature of Cowden syndrome, thereby fulfilling the diagnostic criteria for this condition.[4]

Sequencing of the *PTEN* gene in a DNA sample from lymphocytes of this woman identified a frameshift mutation, c.302-304delTCAinsCC. This woman's mutation was previously reported in detail elsewhere (case *CDve* in Marsh *et al*[5]). Mutation analysis of DNA from other tissues was not carried out.

The woman had presented with acute pain in the right iliac fossa at the age of 32 years. At laparotomy a haematoma involving the broad ligament, ovary, and fallopian tube on the right side was resected. The aetiology of the haematoma was not identified at operation or on pathological review of the resected tissue.

She presented again at 56 years of age with a two month history of pain in the left groin. On clinical examination she had a mass in the left buttock with warm dilated veins in the left groin and extending over the lower abdominal wall and right buttock. Magnetic resonance imaging revealed a vascular mass in the left side of the pelvis with feeder vessels arising from the superior gluteal vessels; the mass extended through the sciatic notch into the left buttock. A subsequent angiogram confirmed the diagnosis of a large gluteal AVM on the left side (fig 1). After two attempts to embolise the feeder vessels she developed a local patch of cutaneous erythema, possibly from impaired perfusion. Her predominant symptom was pain, and this slowly settled with analgesic treatment over a number of months. A repeat angiogram four years later documented a 5 cm lesion in the left gluteal region with central degeneration and calcification. She described persistent discomfort that was stable and not disabling.

Case 2 (GF11097-19)

The sister of case 1 had numerous hyperkeratoses on her arms and hands, macrocephaly (head circumference on 95th centile corrected for height), ductal carcinoma in situ of the breast, and a multinodular goitre. These features constitute one pathognomonic criterion, two major criteria, and one minor criterion, and are sufficient for the diagnosis of Cowden syndrome.[4] DNA studies documented that she had the same *PTEN* mutation as her sister.

This woman presented with pelvic discomfort and dyspnoea at 56 years of age. The sisters are not twins and the

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Abbreviations: AVM, arteriovenous malformation; OMIM, Online Mendelian Inheritance in Man
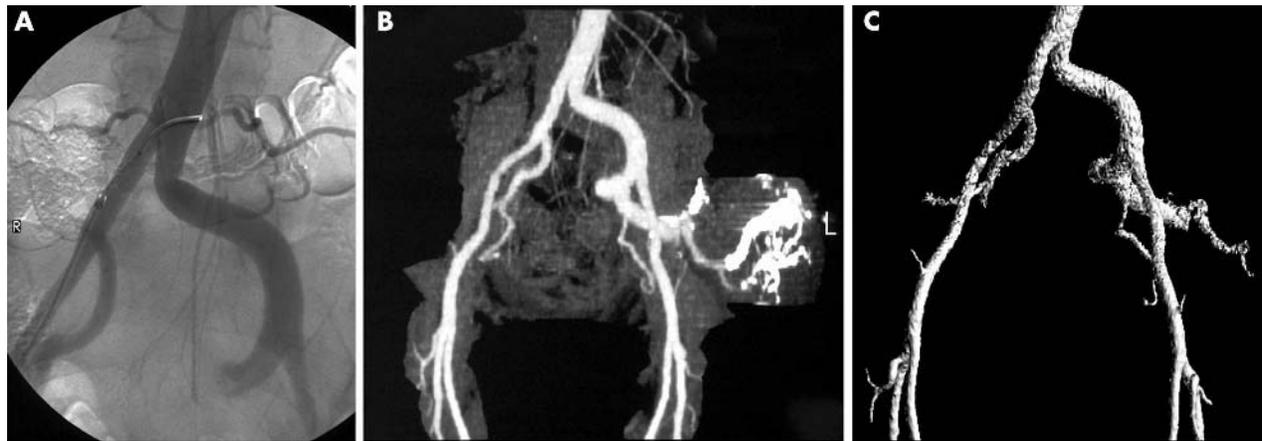
Figure 1 Imaging of the gluteal arteriovenous malformation (AVM) in case 1. All views are in anterior-posterior orientation. (A) Angiogram of the distal aorta and iliac vessels showing the dilated left common iliac and left internal iliac arteries. (B) Computed tomographic angiogram showing a large AVM arising from the left superior gluteal artery and extending through the sciatic notch into the left buttock. (C) A reconstructed rendered surface angiogram showing the AVM arising from the left superior gluteal artery.

similarity in age at presentation was a coincidence. Pelvic computed tomography and angiography showed a large AVM arising from the right internal iliac and inferior mesenteric arteries, with rapid arteriovenous shunting (fig 2). The malformation extended around the broad ligament and uterus on the right side and into the wall of the bladder. She subsequently developed episodic haematuria. Repeated embolisations had limited success in modifying her symptoms and had no impact on the size or apparent shunting in the AVM.

Another sibling sought presymptomatic genetic testing for the mutation and was shown to be a carrier; this sibling did not have a history suggestive of an AVM. Further clinical and genetic studies in this family were not feasible. Two other family members at 50% risk of having the same mutation also had AVMs but were not assessed by the clinical genetics service and did not seek genetic testing. One was reported to have macrocephaly, a multinodular goitre, an intraductal papilloma of the breast, multiple fibroadenomata of both breasts, and an AVM measuring 20×12×25 mm resected from her thigh. The pathology was reported to be a benign AVM with no endothelial proliferation or atypia. The other relative was reported to have had two small AVMs resected from hand and foot at 22 years of age; in each case the pathology was reported to be a benign AVM.

DISCUSSION

AVMs and haemangiomas are not widely recognised features of Cowden syndrome. There are brief comments regarding cutaneous haemangiomas in OMIM[1] and in a review of the clinical features of Cowden syndrome in childhood.[6] There is no mention of other vascular malformations in OMIM or in the current diagnostic criteria for Cowden syndrome.[4]

However, there were a few early reports of significant AVMs in individuals with clinical diagnoses of Cowden syndrome. Three cases reported during the 1970s had visceral or clinically significant AVM—that is, an arteriovenous fistula in the fifth finger of a 13 year old boy,[7] an extensive AVM on the back of a 36 year old woman causing marked circulatory shunting,[8] and a large AVM in the groin of a 25 year old patient.[9] Since then, the genetic literature has focused on the many other features of Cowden syndrome but AVMs have received little attention.

More recently, cases of large AVMs in Cowden syndrome and Lhermitte–Duclos syndrome have been reported in nongenetic journals. Takaya et al[10] described the management of a patient with a clinical diagnosis of Cowden syndrome who presented with multiple large AVMs at the age of 30 years. The lesions caused high output cardiac failure and the patient died. Two patients with Lhermitte–Duclos syndrome and large AVMs have recently been described.[11 12]
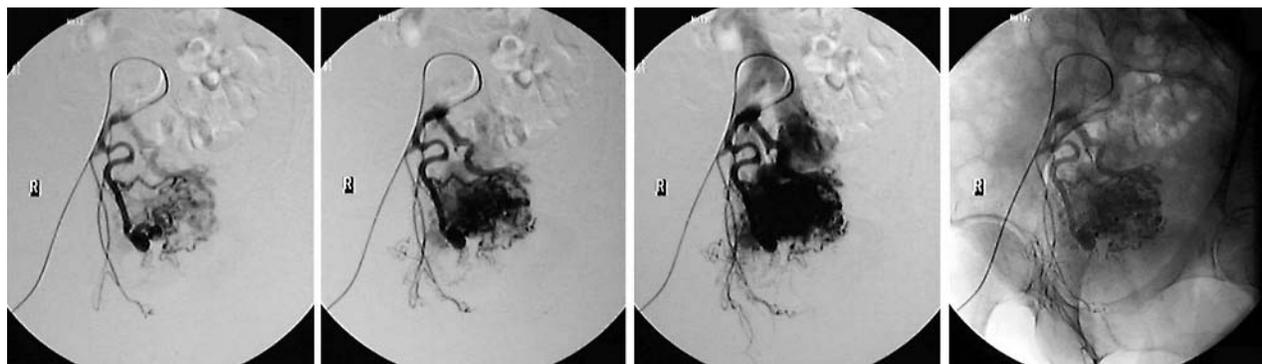

Figure 2 Digital subtraction angiogram of the pelvic arteriovenous malformation (AVM) in case 2. All views are in anterior-posterior orientation. The four views in sequence from left to right show filling of the AVM, predominantly from the right internal iliac artery, and drainage into the right iliac vein and inferior vena cava.

Haemangiomata and AVMs are recognised features of Bannayan–Riley–Ruvalcaba syndrome.[1] Identical *PTEN* mutations have been documented in patients with clinical features of Cowden syndrome or Bannayan–Riley–Ruvalcaba syndrome, both in different families and within the one family.[5] The haemangiomata in Bannayan–Riley–Ruvalcaba syndrome are typically cutaneous and haemodynamically insignificant, but there have been occasional reports of large visceral AVMs.[13–16] There are some phenotypic features in common with Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome, particularly the features of macrocephaly, multiple lipomata, and hamartomata. On the other hand, there are also striking phenotypic differences, with severe intellectual disability and cutaneous haemangiomata being rarely noted in Cowden syndrome. The extent to which these differences and similarities reflect ascertainment bias rather than biological effects is not known.

The present description of relatives with Cowden syndrome and clinically significant AVMs suggests that it may be appropriate to regard visceral AVMs as one of the features held in common by Cowden and Bannayan–Riley–Ruvalcaba syndromes. The family's mutation, c.302-304delTCAinsCC, is a frameshift mutation at codon 100. This mutation has not been described in any other kindred, but truncating mutations distal to this codon have been identified both disorders. At present there are insufficient data to speculate on possible genotype–phenotype associations.

The pathogenesis of the AVMs in these syndromes is unknown. Are these congenital malformations that lie dormant for years before causing symptoms or signs? Or does the vascular malformation evolve over time and hence represent a form of neoplasm? The histopathology noted in the AVMs from two of the relatives described above would argue against a neoplastic process, but this does not preclude a non-congenital process that had evolved over many years.

The association of *PTEN* mutations and AVMs is consistent with the growing evidence that *PTEN* is involved in modulating angiogenesis. The *PTEN* gene is expressed in vascular smooth muscle cells[17] and has an antiangiogenic effect.[18] Hence functional loss of one *PTEN* allele owing to a constitutional mutation and loss of the other allele due to somatic mutation in vascular smooth muscle is the likely but unproven basis of AVMs in Cowden syndrome. *PTEN* downregulates new vessel formation through suppression of VEGF expression[19] and this may provide an avenue for therapeutic suppression of angiogenesis.[20] As evidenced by both the published reports and our own experience, embolisation often fails to control the haemodynamic consequences of large AVMs in Cowden syndrome, and other therapeutic strategies may ultimately prove to be more effective.

The observation that *PTEN* mutations can predispose to the development of large visceral AVMs in two pleomorphic syndromes also raises the possibility that the *PTEN* gene may be implicated in other conditions characterised by AVMs. Zhou et al[21] described a germline *PTEN* mutation in a boy with multiple large AVMs and features suggestive (but not diagnostic) of Proteus syndrome. There have been reports of multiple hamartomatous colonic polyps (described as ''juvenile polyposis'') and AVMs of the lung, liver, or brain. Hamartomatous polyposis and AVMs are features of Cowden syndrome, and *PTEN* could have been considered a candidate gene for this disorder. But a recent report has documented *SMAD4* mutations in patients with juvenile polyposis and hereditary haemorrhagic telangiectasia.[22]

The clinicians who manage the clinical care of people with germline *PTEN* mutations, whether it be in the context of Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, Lhermitte–Duclos syndrome, or Proteus syndrome, should be aware of the risk of haemodynamically significant AVMs developing in these conditions. The challenge in managing these vascular lesions lies in picking the stage at which the AVM is sufficiently symptomatic to warrant intervention yet not too large to limit the efficacy of excision or embolisation. To be forewarned is to be forearmed in managing these difficult lesions.

ACKNOWLEDGEMENTS

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Competing interests: none declared

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