Arteriovenous malformations in Cowden syndrome

M M Turnbull, V Humeniuk, B Stein, GK Suthers

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.

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 CDv in Marsh et al). 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 mass 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.3 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

Abbreviations: AVM, arteriovenous malformation; OMIM, Online Mendelian Inheritance in Man
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 and in a review of the clinical features of Cowden syndrome in childhood. There is no mention of other vascular malformations in OMIM or in the current diagnostic criteria for Cowden syndrome.

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, an extensive AVM on the back of a 36 year old woman causing marked circulatory shunting, and a large AVM in the groin of a 25 year old patient. 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 non-genetic journals. Takaya et al 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.
Haemangioma and AVMs are recognised features of Bannayan–Riley–Ruvalcaba syndrome. 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. The haemangioma in Bannayan–Riley–Ruvalcaba syndrome is typically cutaneous and haemodynamically insignificant, but there have been occasional reports of large visceral AVMs. 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 haemangioma 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 and has an antiangiogenic effect. 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 and this may provide an avenue for therapeutic suppression of angiogenesis. 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. 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.

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.

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Authors’ affiliations
M M Turnbull, G K Suthers, South Australian Clinical Genetics Service, Women’s & Children’s Hospital, North Adelaide, South Australia
V Humeniuk, Department of Surgery, The Queen Elizabeth Hospital, Woodville, South Australia
B Stein, Ashford Cancer Centre, Ashford Hospital, Ashford, South Australia
G K Suthers, Department of Paediatrics, University of Adelaide, Adelaide, South Australia

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Correspondence to: Dr Graeme Suthers, Familial Cancer Unit, SA Clinical Genetics Service, Women’s & Children’s Hospital, North Adelaide SA 5006, Australia; suthergs@mail.wch.sa.gov.au

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