Unusual association of diseases/symptoms

Proliferative retinopathy in Cowden syndrome

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Correspondence to Mr Qasim Mansoor, mans_qasim@yahoo.com**Summary**

Cowden syndrome is a multiple hamartoma syndrome with a high risk of breast and thyroid tumours, both benign and malignant. The authors report a 24-year-old female patient who presented with reduced vision in both eyes. Ocular examination showed vitreous haemorrhage secondary to retinal new vessels in both eyes. There was no evidence of diabetes mellitus, and she had a wide range of normal investigations. She was labelled as idiopathic retinal neovascularisation. Fifteen years later, she presented with a lump in her left breast and a previous history of excision of a benign lump from her right breast. She also reported multiple tumours in her family. Clinical diagnosis of Cowden syndrome was made and genetic testing confirmed mutation of the PTEN gene.

BACKGROUND

We report a patient who presented with a florid idiopathic vasoproliferative retinopathy and then later developed multiple tumours and was confirmed as having Cowden syndrome after genetic testing for the PTEN gene mutation. This is the first case report of Cowden syndrome presenting with isolated retinal neovascularisation in the absence of other eye disease. These findings are consistent with research showing that PTEN plays a role in regulating vascular endothelial growth factor (VEGF)-regulated angiogenesis.

CASE PRESENTATION

In December 1990, a 24-year-old female was referred with recent onset blurred vision in the right eye. She had no previous ophthalmic history and was systemically well. There was also no family history of any eye diseases. Visual acuities were 3/60 right eye and 6/18 left eye. Posterior segment examination showed bilateral active retinal neovascularisation with vitreous haemorrhages in both eyes (figure 1). There was no evidence of diabetes mellitus, and she had wide range of investigations, all of which were normal. She was labelled as idiopathic retinal neovascularisation.

The patient was treated with bilateral panretinal photocoagulation and pars plana vitrectomy (figure 2). Her

vision and retinal status stabilised with acuities of 6/9 in the right eye and counting fingers in left eye after subsequent cataract surgery. In 2010 she was referred with a painless lump in her left breast for 2 months. She had a history of a previous benign right breast lump and thyroidectomy for a benign goitre 3 years ago. Family history revealed that her sister had had breast cancer at the age of 43 and her daughter a renal cell carcinoma at the age of 18 years. Biopsy showed an invasive carcinoma of the breast and after treatment with local excision, radiotherapy and tamoxifen went into remission.

On the basis of presence of multiple benign and malignant tumours and her family history, a clinical diagnosis of Cowden disease was made. Genetic testing confirmed a PTEN (phosphatase and tensin homolog on chromosome 10) gene mutation. Macrocephaly, a feature of the syndrome was also noted.

INVESTIGATIONS

- ▶ In 1990, the following investigations were done to diagnose the cause of the retinal neovascularisation.
- ▶ Full blood count, erythrocyte sedimentation rate, blood glucose, lipid profile, liver function tests, urea and electrolyte, thrombophilia and haemoglobin screen, auto immune screen, venereal disease research laboratory,

Figure 1 Active retinal neovascularisation in right and left eyes.

Figure 2 Inactive disease after extensive pan-retinal photocoagulation vitrectomy.

glucose tolerance test, fundus fluorescein angiography (FFA), carotid ultrasounds and a full cardiovascular assessment.

- All the above investigation were normal. FFA showed early hyper fluorescence confirming the retinal new vessels but importantly there were no areas of vasculitis or capillary drop out.
- In 2010, she had a mammogram and tissue biopsy of her breast lump confirming invasive carcinoma of breast.

DIFFERENTIAL DIAGNOSIS

- Diabetic retinopathy
- Veno-occlusive retinopathy
- Ocular ischaemic syndrome
- Retinal vasculitis
- Other retinal vascular occlusive retinopathies including haemoglobinopathies and coagulopathies.

DISCUSSION

Cowden syndrome is inherited as autosomal dominant with variable penetrance and expression.¹ Patients with this condition are at higher risk of developing a variety of benign and malignant cancers. The risk of developing breast cancer has been estimated at 25–50%.² Non-medullary thyroid carcinomas are the second most common tumour seen.^{3–4} The PTEN tumour suppressor gene is a dual specificity phosphatase with multiple and as yet incompletely understood roles in cellular regulation.¹ It appears to play a significant role in a number of molecular pathways regulating cellular proliferation, migration and apoptosis. Reports of ocular manifestations are sparse, but recently Zaey TJ *et al* described a case of combined hamartoma of retina and retinal pigment epithelium along with papilloedema and hamartoma in the cerebellum (Ihermite-duclos disease).⁵ Meniconi reported a patient with Cowden syndrome who also had chronic uveitis complicated by retinal detachment and glaucoma.⁶ In this case there was some preretinal fibrosis reported – a well-known complication of retinal detachment associated with chronic uveitis – but there was no distinct retinal neovascularisation reported. The exact association between the preretinal fibrosis and the Cowden syndrome remains unknown but it is interesting to postulate that the preretinal fibrosis found in the patient represented

an exaggerated cellular response to the uveitis and retinal detachment secondary to the PTEN mutation. In contradistinction our patient developed retinal neovascularisation as a primary event in the absence of any other eye disease which was complicated by vitreous haemorrhage and preretinal fibrosis. Although the precise role of the tumour suppressor gene, PTEN in angiogenesis is yet to be elucidated it has been shown to downregulate phosphatidylinositol 3-kinase signalling.⁷ This in turn is also a target of VEGF, a known potent stimulus for intraocular angiogenesis and hence provides a possible aetiology and explanation for the retinal neovascularisation observed in our case.

Learning points

- This is a rare case of Cowden syndrome presenting with retinal neovascularisation.
- These findings are consistent with research showing that PTEN plays a role in regulating VEGF-regulated angiogenesis.
- The diagnosis of Cowden syndrome should be considered in patients presenting with proliferative vascular retinopathy and multiple systemic tumours particularly those of the breast and thyroid.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Pilarski R.** Cowden syndrome: a critical review of the clinical literature. *J Genet Couns* 2009;**18**:13–27.
2. **Hanssen AMN, Fryns JP.** Cowden syndrome. *J Med Genet* 1995;**32**:117–19.
3. **Carlson HE, Burns TW, Davenport SL, et al.** Cowden disease: gene marker studies and measurements of epidermal growth factor. *Am J Hum Genet* 1986;**38**:908–17.
4. **Starink TM, van der Veen JP, Arwert F, et al.** The Cowden syndrome: a clinical and genetic study in 21 patients. *Clin Genet* 1986;**29**:222–33.
5. **De Zaeytj J, Bano G, Hodgson S, et al.** A novel association of Cowden syndrome and combined hamartoma of retina and retinal pigment epithelium. *Acta Ophthalmol* 2010;**88**:s245.
6. **Margherita EM.** Uveitis and Glaucoma in Cowden Syndrome. Therapeutical challenge: http://www.uveitis.org/medical/articles/case/Cowden_sy.html
7. **Huang J, Kontos CD.** PTEN modulates vascular endothelial growth factor-mediated signaling and angiogenic effects. *J Biol Chem* 2002;**277**:10760–6.

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