

Large Forehead Nodule with Multiple Facial and Oral Papules

A 25-year-old male presented with an asymptomatic nodule on his forehead. It first appeared 2 years ago and gradually enlarged with time. Physical examination revealed a 13 mm x 15 mm smooth solitary skin-coloured nodule on his forehead (Fig. 1a). He also had several skin-coloured papules on his nose and over his left periocular region (Fig. 1b), oral papillomatosis on his tongue (Fig. 1c) and gums (Fig. 1d) and acral keratosis on bilateral palms (Fig. 1e) and soles. Further examination revealed macrocephaly with an occipital frontal circumference measuring 64 cm and macular pigmentation on glans penis. There were no neurological deficits or cerebellar signs. There were no organomegaly, breast masses, thyroid nodules or palpable lymph nodes. There were also no constitutional or systemic symptoms. Family history was significant for breast cancer in his mother, diagnosed in her 40s. There was no other personal or family history of malignancy. An excision biopsy of the forehead nodule was performed and sent for

histopathologic analysis (Fig. 2). A diagnostic punch biopsy of a nose papule was also performed.

What is your diagnosis?

- A. Darier disease
- B. Cowden syndrome
- C. Birt-Hogg-Dubé
- D. Brooke-Spiegler syndrome
- E. Tuberous sclerosis

Discussion

Cowden syndrome is a rare autosomal dominant disorder first reported in 1963 by Lloyd et al.¹ It is one of the clinical entities in a group of rare syndromes collectively known as phosphatase and tensin homolog (PTEN) hamartoma tumour syndrome (PHTS), characterised by multiple hamartomatous tumours. Mutations in the PTEN gene, a

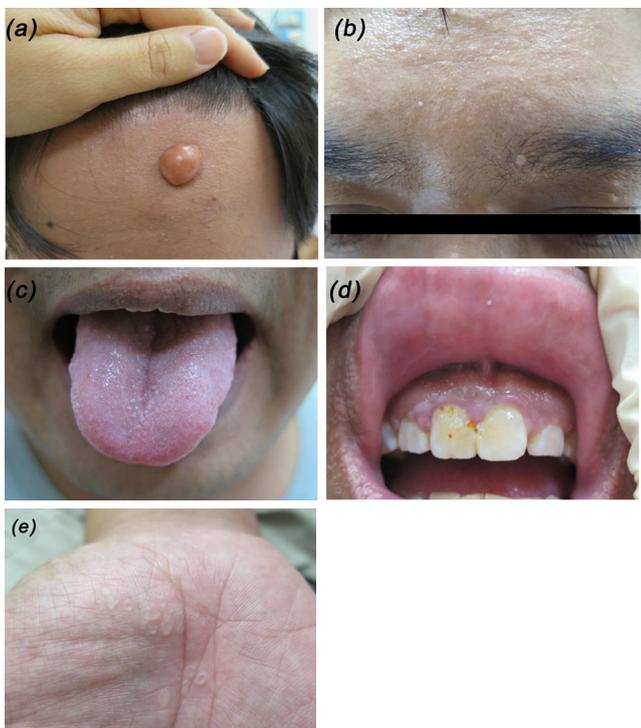


Fig 1. a) Large nodule on forehead; b) facial papillomas; c,d) oral papillomatosis in tongue and gums; e) acral keratoses.

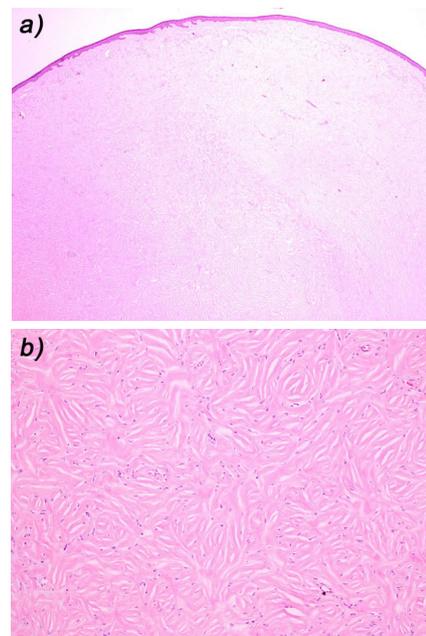


Fig. 2. Excision biopsy of the forehead nodule: a) low power view (x 20 magnification) of a well circumscribed hypocellular nodular fibrous tumour that is composed of collagenous fibres; b) high power view (x 400 magnification) of a prominent storiform growth pattern with elongated clefts between the collagenous bundles, which is characteristic of this tumour.

Answer: B

tumour suppressor gene, results in the dysregulation of the phosphatidylinositol 3-kinase-AKT and mammalian target of rapamycin (mTOR) signalling pathways. This results in dysfunction of cell proliferation, cell cycle progression, and apoptosis, overall contributing to oncogenesis.²

The International Cowden Consortium diagnostic criteria proposed by an international group of experts is categorised into pathognomonic criteria, major criteria and minor criteria³ as presented in Table 1.

Our patient fulfilled operational diagnostic criteria for Cowden syndrome—he had multiple cutaneous facial papules, oral mucosal papillomatosis and multiple palmoplantar acral keratosis bilaterally. In addition, he fulfilled 1 major criteria—macrocephaly ($\geq 97^{\text{th}}$ percentile). He also had macular pigmentation, a feature known to be associated with PTEN mutations. A biopsy of a facial papule (nose) showed a fibrous papule. Although it did not show trichilemmoma, he had fulfilled the other criteria described above. An excision biopsy of the forehead nodule was performed and closed with an advancement flap. Its

histopathological examination was consistent with a sclerotic fibroma. Sclerotic fibroma, or storiform collagenoma, is an uncommon cutaneous neoplasm first reported in 1972 by Weary et al.⁴ It is characterised histologically by a well circumscribed and non-encapsulated dermal nodule comprising hypocellular sclerotic collagenous bundles with prominent clefts. Although it may occur as a sporadic tumour, there is a known association with Cowden syndrome which further supports the diagnosis in our patient.

As the facial papules were benign and asymptomatic, and the patient was not concerned with his cosmetic appearance, they were left alone. As per screening guidelines advocated by National Comprehensive Cancer Network (NCCN),³ we completed a full clinical examination with a baseline thyroid ultrasound scan and educated him on the signs and symptoms of cancer. He was also referred to our gastroenterology colleagues for endoscopic evaluation. Last but not least, he was referred to the adult's genetic clinic for counselling and family screening. He underwent genetic testing which showed a deleterious mutation in PTEN gene, confirming the diagnosis of Cowden syndrome.

Table 1. International Cowden Consortium Diagnostic Criteria

Pathognomonic Criteria	Major Criteria	Minor Criteria
1. Mucocutaneous lesions - facial trichilemmomas - acral keratosis - papillomatous lesions	1. Breast carcinoma	1. Other thyroid lesions (adenoma or multinodular goitre)
2. Lhermitte-Duclos disease (adult)	2. Thyroid carcinoma (especially follicular)	2. Mental retardation (IQ ≤ 75)
	3. Macrocephaly (occipital frontal circumference $\geq 97^{\text{th}}$ percentile)	3. GI hamartomas
	4. Endometrial carcinoma	4. Lipomas
		5. Fibrocystic disease of the breast
		6. Uterine fibroids
		7. Fibromas
		8. Genitourinary tumours or malformations
Operational Diagnosis		
1. Two or more major criteria		
2. One major and 3 minor criteria		
3. Four minor criteria		
4. Mucocutaneous lesions alone in conjunction with: - ≥ 6 facial papules (≥ 3 trichilemmomas) or, - cutaneous facial papules and oral mucosal papillomatosis or, - oral mucosal papillomatosis and acral keratosis or, - ≥ 6 palmoplantar keratosis.		
For Individuals in a Family in which 1 Relative is Diagnostic for Cowden Syndrome		
<ul style="list-style-type: none"> • A pathognomonic criterion • Any one major criteria with or without minor criteria • Two minor criteria • History of Bannayan-Riley-Ruvalcaba syndrome (BRRS) 		

GI: Gastrointestinal; IQ: Intelligence quotient

Several differential diagnoses were considered during the initial evaluation of this patient. Although Darier disease is associated with acral keratosis, oral and facial papules, our patient lacked the characteristic keratotic crusted reddish-brown papules in the seborrhoeic and intertriginous areas. There were no associated nail changes typical of Darier disease. Patients with tuberous sclerosis typically have facial angiofibromas and gingival fibromas, which may appear similar to facial papules and oral mucosal papillomatosis. However, there was a lack of other supporting cutaneous feature such as ashleaf macules, periungual fibromas and Shagreen patch. Thirdly, Birt-Hogg-Dubé may also present with multiple facial and oral papules. However in this case, although the biopsy of the facial papule did not show trichilemmoma, it did not show fibrofolliculoma or trichodiscomas either, both of which are typical of this condition.

There was no history of any lung problems thus far, suggestive of pulmonary cysts which be found in Birt-Hogg-Dubé. Similarly for Brooke Spiegler (although multiple trichoepitheliomas are seen on the central face), the biopsy was not consistent with this.

Our patient did not have any cylindromas or spiradenomas which are seen in this condition. The nodule on the forehead was consistent with a sclerotic fibroma, with a known association with Cowden syndrome.

As Cowden syndrome is a rare clinical entity with an estimated prevalence of 1 in 250,000, it can pose diagnostic dilemmas when encountered. The accuracy of diagnosis is important, especially as this clinical entity is associated with other malignant conditions.

REFERENCES

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