

Case report

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The Birt–Hogg–Dubé syndrome: dermatological features and internal malignancies

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Case report

A 56-year-old Caucasian male presented with a fast-growing subcutaneous tumour on the right shoulder over the last 6 months. On examination, this was a mobile and firm tumour of ~4 cm diameter (Figure 1). The patient was also concerned about cosmetic disfigurement from multiple small facial papules. These had been growing gradually over the last 3 years. The past medical history revealed six episodes of spontaneous pneumothoraces, treated with a right-sided surgical pleurectomy at the age of 28 years, with no recurrence since. Interestingly, his mother had developed identical lesions over her face a few years before she died from an undetermined internal cancer.

Examination revealed dozens of firm whitish small papules distributed on his face (Figure 2), neck and upper trunk. Skin biopsies were consistent with the diagnosis of fibrofolliculomas.

Histopathology of the tumour from the right shoulder showed bland myofibroblastic-looking spindle cells dispersed in a myxoid and collagenous stroma, but elsewhere with an ill-defined storiform pattern and scattered mast cells (Figure 3). Immunostains were negative in lesional cells for S100 protein, epithelial membrane antigen, CD34

cell surface antigen, neurofilaments, desmin, smooth muscle actin antigen, cytokeratin AE1-3, and the MIB-1 proliferation index was low. There was focal nuclear positivity for β -catenin. Overall, the lesion was considered to represent a superficial fibromatosis.

Suspecting a diagnosis of Birt–Hogg–Dubé (BHD), a rare autosomal dominantly inherited genodermatosis, an ultrasound of the abdomen and pelvis was ordered. A mass was identified in the left kidney. Subsequent abdominal and thoracic computed tomography established a 4.5 cm diameter mass at the lower pole of the left kidney (Figure 4) and multiple paraseptal cystic changes throughout the lungs (Figure 4). The patient underwent a successful partial nephrectomy of the left kidney. The histology was consistent with renal cell adenocarcinoma.

The presence of the superficial fibromatosis, a variant of the desmoid tumour described in familial adenomatous polyposis and previous studies showing a link between BHD, colonic polyps and cancer,^{1,2,3} prompted a colonoscopy. This revealed several tubular adenomas at the sigmoid and caecum with three in the caecum exhibiting severely dysplastic changes.

Genetic studies confirmed a mutation of folliculin, a novel protein with tumour suppressor effects.

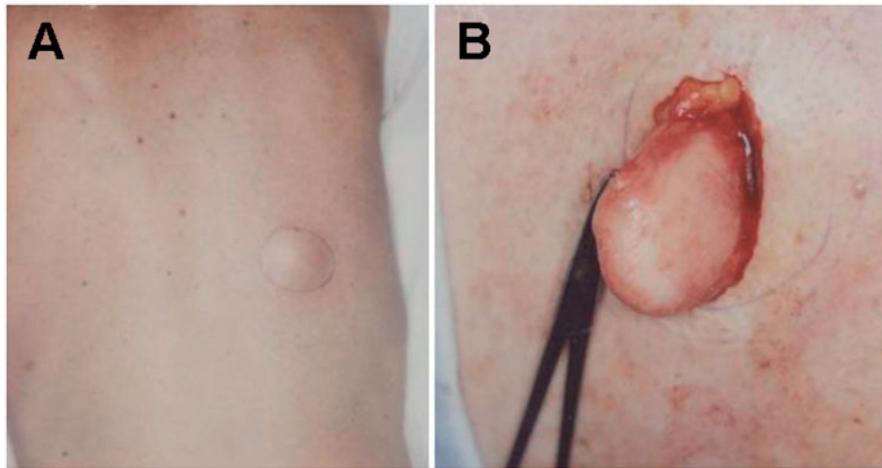


Figure 1. Distant view of the tumour on the posterior aspect of right thorax (A) and at the time of excision (B).

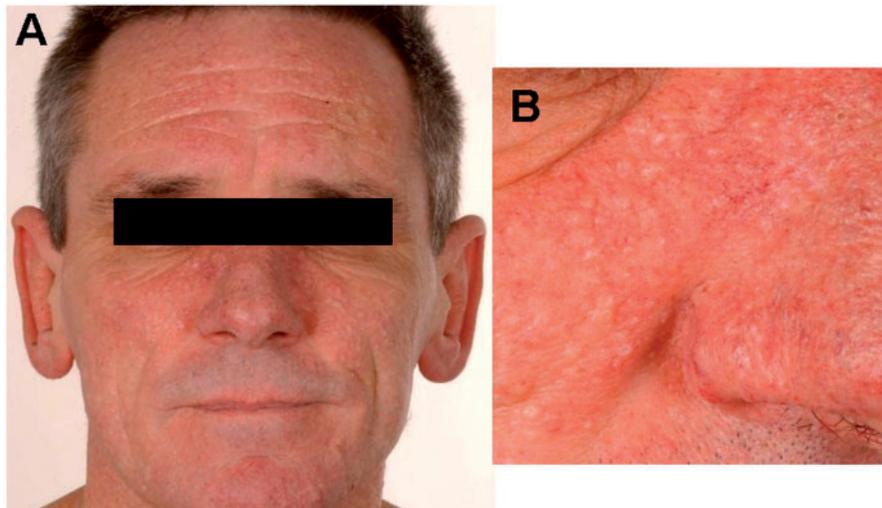


Figure 2. Confluent dome-shaped papules (fibrofolliculomas) on the face (A) and a close-up view of fibrofolliculomas over the right maxillary region and nasolabial fold (B).

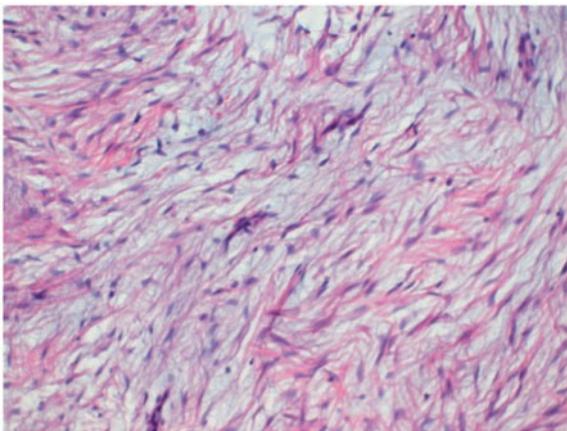


Figure 3. Histopathology of the superficial fibromatosis tumour showing bland myofibroblastic-looking spindle cells dispersed in a myxoid and collagenous stroma (haematoxylin and eosin stain at $\times 200$ magnification).

The actual mutation was shown to be a 4 nt deletion in exon 9 of folliculin gene, c.1345_1348 (p.Glu297fs).

Discussion

The cutaneous features of the syndrome are characterized by benign hamartomas of the hair follicle, which typically develop after the fourth decade as asymptomatic small and firm whitish papules on face, neck and upper trunk. Acrochordon-like lesions very frequently coexist. A recent review supports the idea that these skin tumours represent a spectrum of the same entity, termed fibrofolliculoma.⁴ Angiofibromas, a characteristic tumour of tuberous sclerosis, were also found to be a

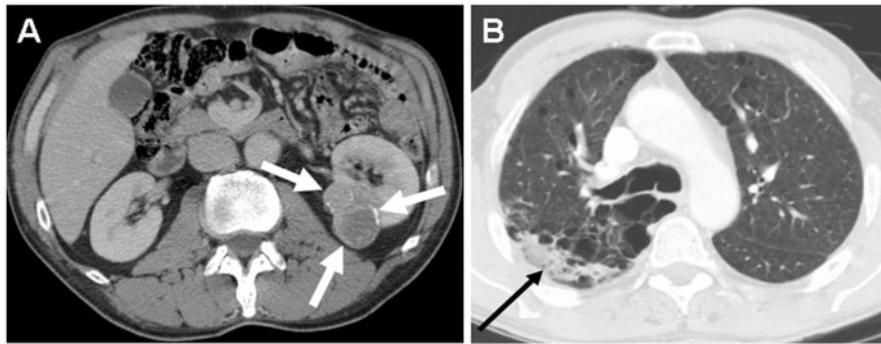


Figure 4. Computerized tomographic scans of the abdomen (A) and thorax (B) illustrating the associated features of the BHD syndrome: renal neoplasm (white arrows) and pulmonary cystic change (black arrow), respectively.

common cutaneous finding in a study of 50 families with BHD.⁵

BHD has a strong association with renal cancers, often multiple and bilateral, and detected at a median age of 51 years.^{5,6} Multiple spontaneous pneumothoraces, due to underlying lung cysts, present at a younger age, often as the first manifestation of the syndrome, as in our case.^{5,6,7}

A number of other cutaneous tumours have been described in patients with BHD syndrome, including multiple lipomas and angioliipomas, neural tissue tumours, cutaneous leiomyoma, cutaneous leiomyosarcoma and dermatofibrosarcoma protuberans.^{5,8,9} However, fibromatosis has not been previously reported. Post-operative fibromatosis-type fibromas have been reported to develop at abdominal surgical sites in heterozygous Nihon rats, a model for the human BHD syndrome. These fibromatosis-type fibromas are the equivalent of human desmoid tumours¹⁰ (described as aggressive fibromatosis), and have also been described in familial adenomatous polyposis (Gardner's syndrome).¹¹

In the past, BHD has also been associated with colonic polyps and colonic neoplasms.^{2,3} Zbar *et al.*⁶ concluded that there was no statistical correlation. In that study, 223 members of 33 BHD families underwent colonoscopy. Of these, three individuals in the BHD-affected group ($n = 111$) had colon cancer, whereas none of the remaining 112 non-BHD-affected group had colon cancer. However, four deceased BHD family members with colon cancer were not investigated for a BHD gene mutation.

Khoo *et al.*³ reported six cases of true neoplastic colonic polyps and two cases of possible colon cancer in a BHD family with confirmed BHD germline mutations, indicating that the BHD gene might be involved in this tumorigenesis. The same team subsequently reported the detection of two novel somatic mutations of the BHD gene and loss of

heterozygosity in 81% of a series of unselected patients with colorectal polyps and cancers.¹

Conclusion

We have identified colonic adenomas with severe dysplastic changes in our patient. We propose that surveillance for colorectal neoplasias should be considered in all patients with BHD.

Additionally, the siblings and children of the proband should be offered genetic counselling and the option to be screened for the presence of this dominantly inherited condition.

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Conflict of interest: None declared.

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