Pulmonary puzzle

ANSWERS
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The combination of cystic lung disease, a family history of lung disease and the characteristic papular lesions on this patient are highly suggestive of Birt-Hogg-Dube syndrome (BHDS). Genetic sequencing of the folliculin (FLCN) gene identified a novel frameshift mutation and confirmed the presence of BHDS.

Cystic lung disease occurs in a relatively narrow disease spectrum including lymphangioleiomyomatosis/tuberous sclerosis complex, Langerhans cell histiocytosis, lymphocytic interstitial pneumonia, neurofibromatosis, Marfan’s syndrome, Ehlers-Danlos syndrome (EDS), α1-antitrypsin deficiency, Pneumocystis jirovecii infection and BHDS. This patient’s strong family history across several generations suggested an autosomal-dominant process such as neurofibromatosis, Marfan’s syndrome, EDS or BHDS. While he did not have the phenotypic characteristics of neurofibromatosis, Marfan’s syndrome or EDS, his skin lesions appeared typical for BHDS. Diagnostic evaluation therefore proceeded to confirm BHDS.

BHDS was initially described in 1977 as an autosomal-dominant disorder of benign skin tumours including fibrofolliculomas, trichodiscomas and acrochordons. Subsequent studies have shown that mutations in the FLCN gene are responsible for BHDS and the gene is highly expressed in skin, kidney and lung stromal cells and type I pneumocytes. A genotype-phenotype association has been reported between the degree of cystic lung disease, the risk of spontaneous pneumothorax and the exonic location of the FLCN mutation.

Although pneumothoraces in BHDS can be associated with morbidity, mortality may be increased in BHDS due to the development of renal tumours (oncocytic hybrid tumours, chromophobe renal cell carcinoma, clear cell carcinoma, papillary renal cell carcinoma). In a cross-sectional analysis of 98 patients with BHDS, the age-adjusted odds ratio for the development of renal cell carcinoma was 6.9, with chromophobe renal cell carcinoma being the most common cell type.

Thus, BHDS consists of characteristic benign skin lesions, cystic lung disease with spontaneous pneumothorax and a risk of renal cell carcinoma. Owing to the potential mortality associated with renal tumours, an annual abdominal CT scan is recommended to evaluate the development of these tumours. Furthermore, due to incomplete skin lesion penetration, family members should be screened with genetic testing or renal ultrasound to check for renal tumours and genetic counselling should be provided to couples planning to have children.

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REFERENCES
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