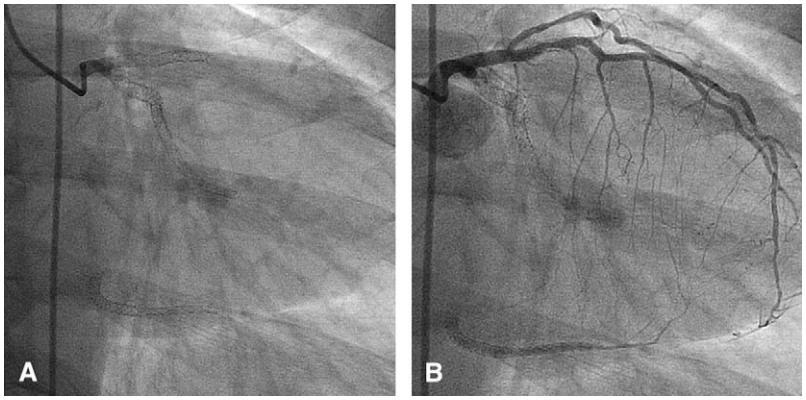

FIGURE 1. Multiple stents in the LAD, OM, and terminal branches of the LCx coronary artery (A), with significant in-stent stenosis in the LAD and complete in-stent occlusion of the OM and terminal branches (B).

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Pneumothorax in two siblings: Is there a genetic basis for recurrence?

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The incidence of primary pneumothorax is reported as 18 to 28 per 100,000 per year for men and 1.2 to 6 per 100,000 per year for women, with approximately 10% having a positive family history.[1] Although recurrent pneumothoraces on the ipsilateral side is seen in less than 5% of cases and may be dependent on the surgical technique, contralateral recurrence may arise because of individual or familial predisposition. Autosomal dominant inheritance of recurrent pneumothorax within families has been associated with the mutation of the folliculin (*FLCN*) gene.[2] Patients who have blebs, bullae, and recurrent pneumothorax with or without a family history may have mutations in this gene.[3] We describe 2 siblings who had multiple ipsilateral and contralateral recurrences despite adequate surgical treatment. In this family, no mutations in the *FLCN* gene were found.

CLINICAL SUMMARY

Patient 1

A 14-year-old girl presented with a small left-sided pneumothorax that was successfully treated with needle aspiration. She returned 2 months later with ipsilateral recurrence and underwent video-assisted thoracoscopic surgery. A left upper third pleurectomy and apicectomy were carried out. Two weeks later, a contralateral right-sided pneumothorax developed, and she underwent right video-assisted thoracoscopic surgery, apicectomy, and pleurectomy. A recurrence on the left side developed 9 months later. Computed tomography showed no pleural bulla or interstitial lung disease. Open thoracotomy revealed a complete regrowth of parietal pleura. A complete pleurectomy was carried out, and she remains well 6 years after the procedure.

Patient 2

The elder brother of patient 1 presented at 17 years of age with a small left pneumothorax that was treated with

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aspiration alone. He presented 1 year later with bilateral pneumothoraces. Bilateral video-assisted pleurectomy and apicectomy were carried out. Histology demonstrated emphysematous blebs apical bullae with no evidence of underlying disease. Eight months later, he presented with a recurrent left-sided pneumothorax that was treated with thoracotomy and pleurectomy. No bullae were seen; however, he presented 5 months later with another recurrence on the left side that was treated with tetracycline pleurodesis. One month later he was readmitted with a right-sided recurrent pneumothorax and treated with a right thoracotomy and pleurectomy. He has remained well for 6 years. Both siblings were of normal stature and build, and had no relevant clinical features of a connective tissue disorder.

GENETIC TESTING

Mutation screening by sequencing of the whole *FLCN* gene in patients 1 and 2 and their unaffected sibling and parents was negative, and no potentially disease-causing mutations were identified.

DISCUSSION

Ipsilateral recurrences are commonly ascribed to surgical techniques. In addition to either open or video-assisted pleurectomy and bullectomy, various other adjuncts, such as covering the staple line with absorbable mesh,[4] talc poudrage, and chemical pleurodesis with blood or tetracycline, are applied to diminish recurrence. However, apart from smoking and the presence of pleural blebs and bullae, genetic factors that are only partly understood may be responsible for recurrences, especially on the contralateral side.

Familial spontaneous pneumothorax is a recognized complication of Marfan syndrome (because of mutations in the fibrillin 1 gene) and has been reported as a dominant trait in families without features of Marfan syndrome or any other connective tissue disorder.[5] In these latter families, molecular genetic testing did not identify any mutations in fibrillin 1, suggesting that another single gene may be involved. In the siblings we report, no features of Marfan syndrome were seen, and therefore analysis of fibrillin 1 was not undertaken. Mutations in the gene encoding *FLCN* located at chromosome 17p11.2 have been found to cause familial recurrent pneumothorax.[2,3] Different mutations in this gene also cause the broader phenotype of Birt-Hogg-Dube syndrome, an autosomal dominant condition with additional manifestations, including skin fibrofolliculomas, thyroid, and renal tumors, as well as recurrent pneumothoraces. Currently, patients with isolated spontaneous pneumothorax and *FLCN* mutations are not known to be at risk of Birt-Hogg-Dube complications, although the genotype–phenotype relationships are not fully understood.[2] In the siblings reported, no *FLCN* mutations were identified, so the basis of their familial predisposition is not clear, but further relevant genes may be identified in the future.

Although recurrence after surgical intervention in part is related to certain modifiable risk factors and surgical techniques, the role of pleural blebs and bullae and the genetic predisposition of individuals and families must be considered. Genetic testing may have a future role in identifying individuals at high risk of pneumothorax, guiding aggressive operative management, and providing genetic information to patients' families.

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