In-Flight Pneumothorax: Diagnosis May Be Missed because of Symptom Delay

To the Editor:

Boyle's law describes the inverse relationship between pressure and volume for gas in a closed system at constant temperature. On the basis of this mechanism, an air-filled lung cyst will increase in size in an environment with a lower atmospheric pressure. Patients with cystic lung disease might therefore be at risk of developing pneumothorax during air travel.

Many persons have cystic changes in the lung, but the incidence of in-flight pneumothorax is low (1). This apparent discrepancy seems at first sight strange, but is in fact what one might expect. Any cystic airspace in the lung will not expand in size if connected to the bronchial tree, because there is no possibility to develop intracystic overpressure. However, if there is no, or a small, connection between an air-filled cyst and the bronchial tree, the cyst will increase in size by 25–30% (2), which may lead to rupture of the cyst. This is not sufficient for developing pneumothorax; the visceral pleura needs to rupture as well. This may occur if a cyst is adjacent to the visceral pleura. Whether this results immediately, with delay, or not at all in a symptomatic pneumothorax should logically depend on the extent of the damage. This may be limited to the cyst wall and covering visceral pleura, but may also involve the surrounding lung tissue. Subsequently this determines the size of the connection between the airways and the pleural cavity and through that the magnitude of transport of air into the pleural cavity. Therefore we hypothesize that a pneumothorax developed during air travel may become symptomatic hours, or more likely days, after air travel.

We here report a patient with Birt-Hogg-Dubé (BHD) syndrome who traveled by air and later developed pneumothorax.

Some of the results of the studies cited have been previously reported in the form of an abstract (3–6).

Case Report

A 38-year-old male was diagnosed to have BHD after his uncle had been diagnosed with facial skin fibrofolliculomas. Three family members were found to carry the same pathogenic FLCN (folliculin) germline mutation; his father and brother are asymptomatic, and the patient's sister had a history of recurrent bilateral pneumothorax. The patient works for a commercial international firm and travels often. The mean number of flights per year during the last 6 years was 12. His first pneumothorax, at the age of 34, was treated by drainage through a chest tube. Within 2 months he developed a contralateral pneumothorax. Bilateral apical pleurectomy was performed. Four years later he flew across the Atlantic. He had no symptoms during or after this flight. The day after arrival he visited one of the world's highest towers and used the speed lift to 410 m in about 45 seconds. After descent to ground level he developed acute serious shortness of breath. Chest X-ray demonstrated a left-sided pneumothorax with collapse in the basal part of the left lung. He flew back to Europe with a Heimlich valve connected to a chest tube and was referred for additional treatment.

As the last event occurred during a rapid change in atmospheric pressure (speed lift) and shortly after a transatlantic flight, on returning home he checked his old diaries for his flight pattern around the earlier episodes of pneumothorax. The first pneumothorax was diagnosed on December 17, 2010. Symptoms had started the day before diagnosis, and he had flown on the 8th and 12th of that month within Europe. At discharge from the hospital there was radiological proof of complete pneumothorax resolution. His contralateral pneumothorax was diagnosed on January 31 after some shortness of breath starting on January 30; he then flew across the Atlantic on the 17th and 21st of that same month.

Discussion

BHD syndrome is inherited in an autosomal dominant manner, and is caused by germline mutations in the *FLCN* gene. It is clinically characterized by facial fibrofolliculomas, pulmonary cysts, recurrent pneumothorax, and increased risk for renal cell cancer (7). All patients with BHD with (recurrent) pneumothorax have pulmonary cysts, especially in the lower lobes. The cysts are located both in the parenchyma and subpleural area. We used computed tomography (CT) to analyze the lungs of 18 other patients with BHD with a history of at least one episode of pneumothorax; all patients had cysts and 50% of all cysts were located in the subpleural area (3). Small subpleural cysts might have been missed on a standard CT (8). Several studies on the role of atmospheric pressure changes have shown that after the trigger event (assumed to be a change in atmospheric pressure), some delay in admission of patients with a spontaneous pneumothorax often occurred (9). For instance, Scott and colleagues reported a delay of up to 4 days after a significant change in atmospheric pressure (10). For the current patient, considering the pressure changes during subsequent flights as the potential trigger for initiating rupture of a subpleural cyst, implies that the interval between air travel and the diagnosis is, respectively, 5 and 9 days (first episode), 10 and 14 days (second episode), and 2 days or immediately after use of a speed lift (third episode of pneumothorax). The latter gives a much faster change (68 hectopascals [hPa]/min) in outside pressure than during ascent ($<$13.3 hPa/min) in commercial air travel (11) and might cause a rupture of a cyst by itself or, more likely, based on the start of the patient's symptoms, aggravate a small pneumothorax that could have developed during the flight 2 days earlier. Hoshika and colleagues reported no relationship between development of spontaneous pneumothorax and 2,142 flights among 48 patients with BHD (4). Three patients reported tightness of the chest. Unfortunately, there were no details on the length of time after flying and the moment their patients became symptomatic because of the pneumothoraces; this makes it uncertain whether there might have been a possible delay after the pressure change as in our patient. It was striking to note the reduction in number of flights in this series after the patients became aware of the underlying cause.

One of the hallmarks of pneumothorax in patients with BHD is the high recurrence rate, 59% in 53 cases (5). Rupture of a subpleural cyst is the likely cause of the pneumothorax in

Author Contributions: Concept and design, P.E.P., P.C.J., F.H.M., and M.A.P.; interpretation, P.E.P., P.C.J., F.H.M., and M.A.P.; drafting manuscript, P.E.P.; revising manuscript, P.C.J., F.H.M., and M.A.P.

patients with BHD. These cysts are found in the subpleural area, suggesting that treatment to prevent recurrence should aim at pleurodesis of the whole pleura visceralis, not only in the apical region. This can be done by extensive pleurectomy and/or talc pleurodesis. From this perspective the initially performed bilateral apical pleurectomy is inadequate as was also found in our retrospective series (5).

Kumasaka and colleagues (12) analyzed resected lung specimens of 50 patients with BHD. Of 229 cysts that were found, 50% were located in the subpleural area and less than 5% abutted on bronchioles. Subpleural cysts are by definition far from the larger airways, so if a cyst were connected to the bronchial tree the size of the connection to the airways would be small, resulting in only small volumes of air being transported into the pleural cavity. Therefore it will probably take a long time before troublesome symptoms occurred. This concept of delayed symptoms after the actual rupture of a cyst is probably relevant for other diseases with cystic changes in the lung, for example, lymphangioleiomyomatosis or Langerhans cell histiocytosis, assuming there is no (or minimal) connection between airways and cyst. Furthermore, spontaneous resolution of a small pneumothorax after rupture of a subpleural cyst may occur if there is no active transport of gas into the pleural cavity. Evidence that this occurs *in vivo* comes from the presence of inflammation at the pleural side of the majority of the cysts (12, 13) and the demonstration of pleural inflammation in patients with a pneumothorax (14).

In a survey of 190 patients with BHD we found that of the group with a previous pneumothorax, 12 other patients had a total of 13 episodes of pneumothorax within 31 days of a continental or intercontinental flight (6). The interval between flying and diagnosis of pneumothorax was less than 10 days in 6 cases, between 10 and 20 days in 4 cases, and between 20 and 30 days in 3 cases. This supports our hypothesis that the delay in becoming symptomatic should be taken into account if a relation between atmospheric pressure changes and pneumothorax is studied. Consequently, patients with BHD who have minimal chest symptoms after a first flight should be checked for pneumothorax before the return flight, because the presence of a pneumothorax, even if it is small, is a known risk factor for flying (15, 16). At the second pneumothorax our patient flew more than 1 week after documented resolution of the first event, in line with British Thoracic Society (BTS) guidelines. However, the character of the pulmonary abnormalities of BHD makes it questionable whether current BTS guidelines on pneumothorax and flying are applicable for these patients (16). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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