Pneumomediastinum and Striking Family History: Uncommon Case of Birt-Hogg-Dubé Syndrome

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Abstract

Birt-Hogg-Dubé syndrome is a rare autosomal dominant condition caused by a germline mutation in the folliculin gene, which is characterized by skin fibrofolliculomas, multiple lung cysts and renal cancer. The clinical expression of the syndrome is highly variable, with recurrent pneumothoraces due to ruptured lung cysts in many cases. We report a patient with pneumomediastinum and cervico-facial emphysema after severe coughing without pneumothorax, skin lesions or renal tumour, but a striking family history of lung abnormalities.

Key words: Birt-Hogg-Dubé syndrome, genetic disorder, pneumomediastinum

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Introduction

Pneumomediastinum with subcutaneous emphysema is a frequent reason for visits to the emergency department; it is the result of a wide range of underlying diseases. Pathophysiologically free air gets into the cervical or thoracic interstitial space and can extend along defined compartments from the neck down to the retroperitoneal space. The entrance may be a defect or tear anywhere in the air-filled organs of the upper or lower respiratory or the upper gastrointestinal tract. History is very helpful in many cases to identify causes such as traumatic or iatrogenic causes. Spontaneous pneumomediastinum is defined in the absence of traumatic or iatrogenic causes and preceding severe pulmonary pathology, and usually is a benign entity. In most cases pneumomediastinum is due to rupture of alveolar septa after dramatic increase of intrapulmonary pressure occurring during prolonged Valsalva manoeuvre such as coughing, strenuous sport, labour or use of inhaled drugs (1). Free air extends along peribronchial and perivascular spaces into the mediastinum and subcutaneous compartments in half of the cases.

We report a patient with pneumomediastinum and cervico-facial emphysema after severe coughing and a striking family history of pneumothoraces.

Case Report

A 23-year-old man was hospitalized with discrete swelling of the face, pain in the upper thorax and a nasal voice. The patient reported a cold for 6 days with severe coughing. The medical history was unremarkable except for smoking (10 pack-years) started at the age of 16; there was no particular history of trauma or surgery in the preceding days. Initial physical examination showed extensive subcutaneous emphysema from the face down to the upper thorax and initial chest X-ray confirmed subcutaneous emphysema of the neck, upper thorax and axillary region without evidence for rib fracture. Computed tomography (CT) of the chest and neck performed at the same day demonstrated air in the subcutaneous and visceral spaces of the neck extending down to the mediastinum without evidence of pneumothorax and additionally, a single cyst in the right middle lung field (Fig. 1). There was no clinical or laboratory evidence for infection or Boerhaave syndrome. Results of flexible bronchoscopy, gastrografin swallow study and otolaryngology examinations were normal without evidence for a leakage or perforation.

The patient reported that seven additional family members had had “lung problems” in the past. The patients general practitioner was contacted and confirmed spontaneous pneu-
mothoraces with or without detected lung cysts in four (II-1, II-8, III-1 and III-10) and lung “abnormalities” not further clarified in three of the respective family members (I-2, II-3 and II-7), suggesting an underlying inheritable disease (Fig. 2). There was no clinical evidence for Marfan syndrome and Ehler-Danlos syndrome in our patient, and serum α1-antitrypsin levels were normal, so a potential diagnosis of Birt-Hogg-Dubé (BHD) syndrome was suspected. Sequencing of the FLCN (folliculin) gene revealed a frameshift mutation in exon 4 (c.59delT), which is reported to cause BHD syndrome (Fig. 3) (2). A diagnosis of pneumomediastinum with cervicofacial emphysema secondary to pulmonary manifestation of BHD was made. The rupture of a pulmonary cyst was most likely triggered by heavy coughing.

Discussion

BHD syndrome is an autosomal dominant condition caused by a germline mutation in the FLCN gene, which is characterized by skin fibrofolliculomas, multiple lung cysts and renal cancer (3). There are approximately 270 families worldwide reported to have BHD syndrome. The clinical expression of the syndrome is highly variable, with skin lesions manifest in about 75% of BHD affected adults, multiple basally located lung cysts detectable on CT in 80% of patients and renal cancer occurring most often sporadically. Notably, BHD syndrome is associated with a 50-fold increased risk of pneumothorax, most probably caused by rupture of a lung cyst, with a prevalence of pneumothorax of
Figure 3. Sequence electropherogram of genomic DNA of the patient showing heterozygous status of a frame shift mutation (c59delT [p.Phe20SerfsX35], highlighted yellow, with reference sequence NM_144997.5 at the top) in exon 4 of the FLCN gene. The dark blue bar indicates a sequence not readable due to heterozygous frame shift mutation with consecutive nucleotide miss-match in corresponding chromosomes.

24% (3). Hence, recurrent spontaneous pneumothoraces with or without typical skin lesions are the most frequent clinical manifestation of BHD syndrome reported in the literature (4).

To our knowledge, this is the first case of a patient with BHD syndrome primarily manifesting with pneumomediastinum and cervicofacial emphysema without pneumothorax or typical skin lesions. Spontaneous rupture of peripheral pulmonary alveoli due to sudden increase of intra-alveolar pressure causing pneumomediastinum is not uncommon in healthy young men (5). In general, no further evaluation is required and when occurring for the first time, pneumomediastinum might not point to BHD syndrome. Indeed, our patient did not fulfill any of the major (≥5 fibrofolliculomas or trichodiscomas, at least one histologically confirmed) or minor (multiple bilateral lung cysts, early onset or bilateral or multifocal renal cancer and first-degree relative with confirmed BHD syndrome) clinical criteria recommended for the diagnosis of BHD syndrome (3). The striking family history of “lung abnormalities” with confirmed pneumothoraces in four family members which so far had not been further examined led to the suspicion of an inherited trait and finally to the diagnosis of BHD syndrome. The major clinical impact of BHD syndrome is the 7-fold increased risk of renal cancer with earliest manifestation reported at age of 20 (3). Hence, identification of patients with BHD syndrome is important to initiate screening for renal cancer which is recommended in yearly intervals by ultrasound or MRI and genetic testing of first-degree relatives for mutations of the FLCN gene.

We conclude that the pulmonary manifestation of BHD syndrome might not only be spontaneous or recurrent pneumothorax but also cervicomedial emphysema. Assessing the typical characteristics of BHD syndrome including family history is advisable in all patients with pneumomediastinum and cervicofacial emphysema.

The authors state that they have no Conflict of Interest (COI).

References