A cystic and bullous lung disease associated with a PIK3CA-related overgrowth syndrome

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To the Editors:

Multifocal cystic lung diseases can be due to numerous causes and their diagnosis may be challenging, necessitating a systematic workup. PIK3CA (phosphatidylinositol 3-kinase catalytic subunit α)-related overgrowth syndrome (PROS) is a rare hypertrophic syndrome due to somatic mosaic mutations in the *PIK3CA* gene. These mutations occur in the post-zygotic stage [1] and lead to a hyperactivation of the phosphatidylinositol 3-kinase (PI3K)–AKT–mechanistic target of rapamycin (mTOR) pathways, resulting in an increased proliferation, survival and cellular mobility of the impacted cells. PROS phenotypes are multiple and depend on the mutation location as well as on the time of its post-zygotic occurrence. They share clinical characteristics such as congenital or early childhood onset of abnormal and asymmetric tissue overgrowth (adipose, muscle, nerve and skeletal) [2], vascular and/or lymphatic malformations, and epidermal nevus [3]. Different types of malignant tumours (colon, breast, brain, liver, stomach and lung) [4] have also been described in this context. To our knowledge, PROS-associated pulmonary nonmalignant manifestations have never been reported before. We describe here a patient with a bullous and cystic lung disease diagnosed in the context of a clinically and genetically diagnosed PROS.

A 29-year-old female presented for a progressively worsening dyspnoea, with a modified Medical Research Council scale score of 2 on presentation. She was an active smoker (3 pack-years) and had a history of a deep vein thrombosis of a lower limb. She reported no other medical condition in childhood or young adulthood and was unaware of any fetal development issue or evaluation. She did not take any medication. No significant familial medical history was reported. Physical examination showed a reduced vesicular breath sound predominantly in the right hemithorax without any other respiratory signs or symptoms. Oxygen saturation on room air was 97%. Several extrathoracic abnormalities were observed in this patient with a plane angioma on the right lower limb, a perioral angioma and a macrodactylia (figure 1a–d).

A thoracic computed tomography (CT) scan was performed that showed multiple, bilateral, diffuse and different sized cysts associated with bullous lesions (figure 1e). No previous imaging was available for this patient.

Pulmonary function tests showed a severe and irreversible airflow obstruction (forced expiratory volume in 1 s (FEV_1)/forced vital capacity: 62%; pre-bronchodilator FEV_1: 1000 mL (37% predicted); post-bronchodilator FEV_1: 1360 mL (48% predicted)). The autoimmune biological workup was negative. Serum levels of vascular endothelial growth factor D, immunoglobulin light chains and α_1-antitrypsin were normal. No mutation was detected in the gene encoding folliculin. Abdomen and pelvic CT scanning did not exhibit any renal angiomyolipoma nor lymphangioleiomyoma. Fibreoptic bronchoscopy was discussed but not performed. Indeed, it seemed to us that her respiratory condition, characterised by a severe decline in FEV_1 (37% predicted) and the large extent of radiological lesions, was actually too severe for the risk of post-procedure complications. This is the reason why we opted for a noninvasive diagnostic procedure and referred the patient for a dermatology evaluation. A biopsy of a lower limb plane angioma was performed and subjected to appropriate genetic studies after obtaining informed consent. A *PIK3CA* mosaic mutation (Q546P, variant allele frequency 4%) was detected that allowed us to establish the diagnosis of PIK3CA-related overgrowth syndrome.

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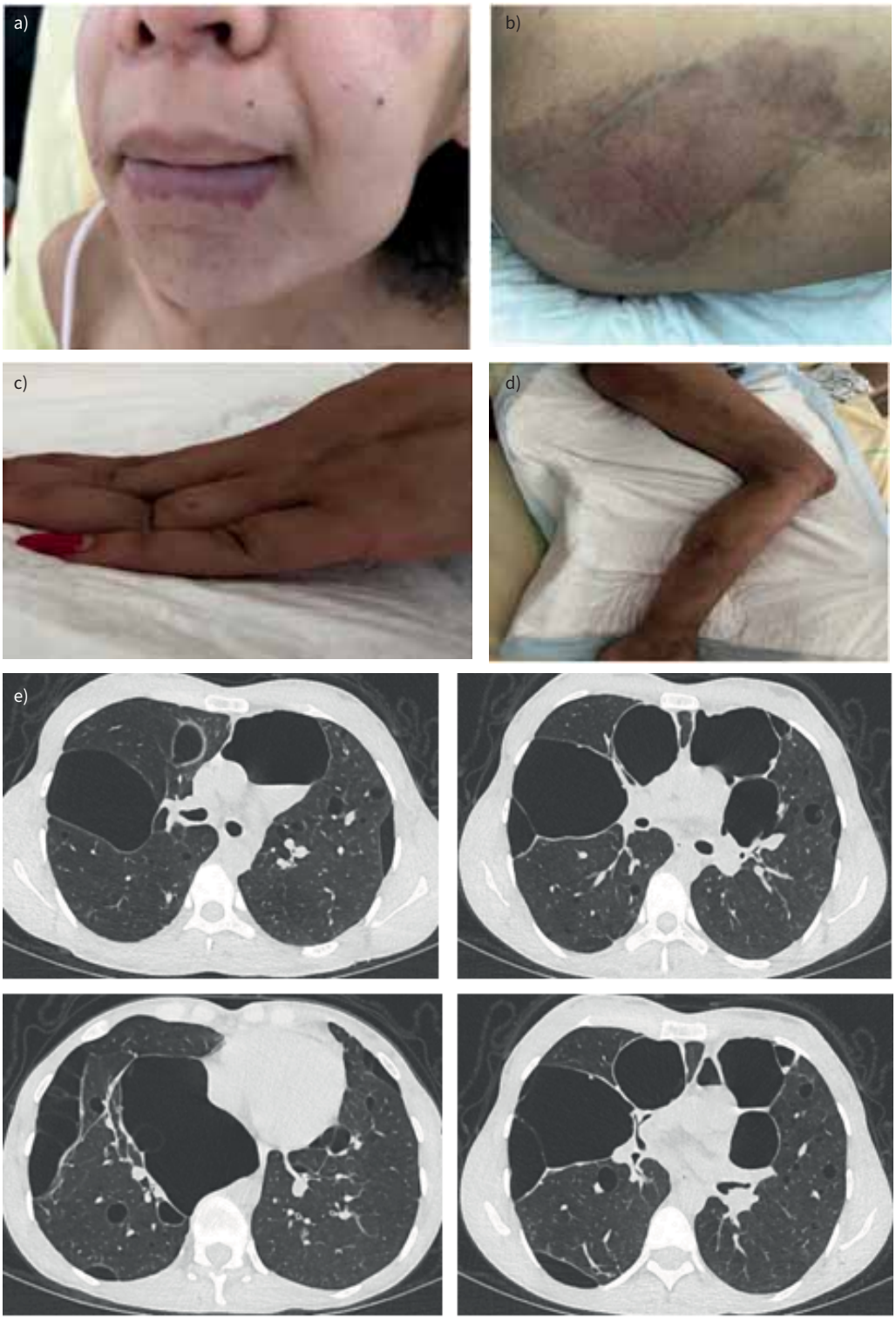

FIGURE 1 Skin lesions. a) Perioral angioma. b and d) Plane angioma (right lower limb). c) Macrodactylia (left hand). e) Axial computed tomography scan.

We report here, for the first time, a respiratory condition associated with PROS, consisting in a severe cystic and bullous lung disease. If aetiologies of multifocal cystic lung diseases in young women are numerous, some cutaneous (café-au-lait spot and fibrofolliculoma) and/or vascular (angiofibromas and Raynaud's phenomenon) abnormalities may be critical hints to the diagnosis, such as in Bourneville

tuberous sclerosis [5], immunoglobulin light chain deposit-associated disease (indurated plaques and purpura for minor trauma), Langerhans cell histiocytosis (skin rash, petechiae and purpura, and erythematous scaly or crusted papules) [6], neurofibromatosis (neurofibroma, café-au-lait spot and lentiginous tumours) or connective tissue diseases (Raynaud's phenomenon and dry eye disease) [7]. In our patient, the presence of multiple angiomas associated with a hand overgrowth was suggestive of PROS. The diagnosis was subsequently confirmed by appropriate molecular investigations.

PIK3CA mutations were not investigated in our patient's lung due to the high risk of bronchoscopy in her severe respiratory condition. However, it is very unlikely that her pulmonary manifestations are related to any other condition considering her negative extensive aetiological workup. In addition, her young age and low cumulative tobacco intake make it also unlikely that tobacco played a central role in her respiratory presentation.

Pathophysiology of pulmonary cysts and bullae development in cystic lung diseases is complex and still largely unknown. We think that our case might contribute to a better knowledge of these conditions though highlighting the potential implication of the PI3K–AKT–mTOR pathways. Indeed, it should be noted that PROS may be associated with extrapulmonary lymphatic cystic malformations [8]. Such lymphatic dysfunctions might be present in our patient and at least partly explain her pulmonary presentation. In addition, Proteus syndrome, another rare overgrowth disorder caused by a somatic activating mutation of *AKT1*, involved in the PI3K–AKT–mTOR pathways [9], is classically associated with bullous or cystic pulmonary lesions. The genetic origin of these two syndromes being quite comparable, we hypothesise that their resulting pulmonary manifestations might also be comparable.

The main activating *PIK3CA* mutations present in PROS are E542K, E545K and H1047R [10]. The cellular mosaicism in which these mutations occur might explain the marked heterogeneity of the involved organs. Finally, it should be noted that our patient had a history of a deep vein thrombosis, which has already been described as a potential clinical manifestation of its associated venous malformations [11].

This condition has had, so far, a bad prognosis and a poor survival. Sirolimus, a mTOR inhibitor, has been evaluated in PROS in an open-label study in three centres and showed a moderate reduction of overgrowth but was associated with a significant number of adverse events (infections, neutropenia, interstitial pneumonitis and sirolimus hypersensitivity syndrome) [12]. Recently, a specific PIK3CA inhibitor, alpelisib, has shown encouraging results in a real-world study in a cohort of 19 PROS patients, such as a clinical improvement of hypertrophic syndromes as well as that of skin and vascular lesions [13]. Furthermore, this treatment was well tolerated. It might therefore represent a considerable therapeutic hope in the very rare PROS condition.

To our knowledge, this is the first description of a cystic lung disease associated with PROS. The natural evolution of lung lesions in the PROS is presently unknown but could largely benefit from innovative treatments such as alpelisib.

Pierre Halitim[1], Jean Pastré[1], Tristan Mirault[2,3], Guillaume Canaud[4,5,6] and Dominique Israël-Biet[4]

[1]Service de Pneumologie et Soins Intensifs, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Paris, France. [2]Université Paris Cité, INSERM, PARCC, Paris, France. [3]Service de Médecine vasculaire, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Paris, France. [4]Faculté de Médecine, Université de Paris Cité, Paris, France. [5]INSERM U1151, Institut Necker-Enfants Malades, Paris, France. [6]Unité d'Hypercroissance Dysharmonieuse et Anomalies Vasculaires, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France.

Corresponding author: Pierre Halitim (pierrehalitim@gmail.com)

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Ethics statement: We have obtained written consent from the patient for publication of her case.

Conflict of interest: P. Halitim, J. Pastré, T. Mirault and D. Israël-Biet have no conflicts to declare. G. Canaud declares a patent application ("BYL719 (alpelisib) for use in the treatment of PIK3CA-related overgrowth spectrum"

#WO2017140828A1) has been filed by INSERM (Institut National de la Santé et de la Recherche Médicale), Centre National De La Recherche Scientifique, Université Paris Descartes and Assistance Publique-Hôpitaux De Paris for the use of BYL719 (alpelisib) in the treatment of *PIK3CA*-related overgrowth spectrum (PROS/CLOVES syndrome). G. Canaud is the inventor. This patent is licensed to Novartis. G. Canaud receives or has received consulting fees from Novartis, Fresenius Medical Care, Vaderis, Alkermes, IPSEN and BridgeBio.

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