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Case report

Type II congenital pulmonary airway malformation associated with intralobar pulmonary sequestration: report of a case and review of classification criteria

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Key words

Congenital cystic adenomatoid malformation • Congenital pulmonary airway malformation • Congenital thoracic malformations • Endoderm/mesoderm interaction • Lung cysts • Pulmonary sequestration

Summary

Pulmonary congenital abnormalities are rare disorders including congenital pulmonary airway malformations (CPAM) and pulmonary sequestration (PS). CPAM is a lesion characterized by the presence of anomalous bronchiolar or acinar structures, variable in size, either cystic or not cystic. PS is generally defined as nonfunctioning lung tissue that is not in normal continuity with the tracheobronchial tree and that derives its blood supply from systemic vessels. We describe a case of a baby girl with a very rare association between CPAM type 2 and intralobar pulmonary sequestration (IPS) focusing on the cystic lesions typical of CPAM and on the lymphatic and blood vessels. The cells lining the cysts often were positive for D2-40 (oncofetal protein M2A). Lymphatic endothelial cells, positive for D2-40, were widely present in the lung parenchyma and dilated lymphatic vessels were present also in the inter-alveolar septa. Moreover, we discuss the pathogenesis of CPAM and its classification criteria.

Introduction

Congenital pulmonary airway malformations (CPAM) and pulmonary sequestration (PS) are lesions included in the spectrum of the "congenital thoracic malformations" (CTMs) [1]. CPAM, called also congenital cystic adenomatoid malformation (CCAM), is a lesion, assumed to be hamartomatous, characterized by the presence of anomalous bronchiolar or acinar structures, variable in size, either cystic or not cystic [2]. It is classified in five main categories on the basis of the prevalent component or, in other words, on the basis of the apparent site of maldevelopment of the airway lesion [3]. This classification system was not widely applied and it has been recently revised[1]. However, CPAM type 2 is characterized by the presence of bronchiolar-like structures forming cysts with a diameter comprised between 0.5 and 2 cm. In 95 % of CPAM type 2 cases only one lobe is affected, with a minimal preference for the inferior ones (55 %). It has a typical paediatric onset and manifests mainly in the newborns as distress respiratory syndrome [3]. PS are localized lesions comprising lung parenchyma receiving their blood supply via aberrant systemic arteries and lacking continuity with the upper respiratory tract [4 5]. PS can be distinguished in extra-lobar (EPS) and intra-lobar (IPS). The former is a pulmonary segment distinct from the normal lung, coated by its own pleura. In the second one, the accessory lung is annexed to the normal parenchyma and shares the same pleura with the normal one [6]. IPS affects the basal lobes in 98 % of cases and, in particular, the posterior basal lobe (81 %) [2]. In addition IPS, differently from EPS, is rare in early childhood. More than one CTM are frequently found in the same patient [6] and this suggests their common pathogenesis. However, the co-occurrence of both CPAM and IPS in the same individual is rare and the pathogenic mechanisms leading to their combination are unclear [7]. In this work we describe a case of a congenital malformation in which CPAM type 2 and IPS are combined. Furthermore, we discuss the pathogenic mechanisms and make a critical review of the classification criteria of CTMs.

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Case report

A baby girl was born by a full term delivery at the Obstetric Unit of Siena University Hospital. At birth she presented an acute respiratory distress syndrome. A chest MDCT (multirow detector computed tomography) showed a multicystic mass localized in the lower lobe of the right lung, with the largest cyst of diameter of 23 mm and presenting an air-fluid level within it. Moreover the mass showed a systemic blood supply from a large arterious vessel originating from the abdominal aorta. Further, the pulmonary arterial vessels of the right lower lobe were interrupted after the origin of the apical branch. A right lower lobectomy was performed at the age of four months. At gross examination, the resected right lower lobe of the lung measured 7 x 5 x 6 cm. A systemic artery (maximum diameter 5 mm) was identified at the congested, red wine colored basal posterior segment located at the transition between thoracic and diaphragmatic surface. This artery branched off in the posterior basal segment of the basal pyramid (Fig. 1a-1b). The cut surface of lung parenchyma showed multiple cysts with a diameter varying between a few millimeters and 2 cm, occupying the entire basal pyramid. Abnormal vessels walls were as thick as those of the systemic arteries. There was no clear separation between the territory perfused by these vessels and the remaining parenchyma (Fig. 1c-1d). At microscopic examination, the walls of the cysts were formed by a central portion rich in blood and lymphatic vessels that were separated from the epithelial component by bundles of smooth muscle. Most of the cysts were lined by a ciliated epithelium (Fig. 2a-2b). The walls of the abnormal arterial branches were thick and contained continuous circular elastic fibers, similar to those seen in systemic elastic arteries. Their branches were directed in a disorganized way towards the posterior basal segment and formed a conglomeration of large vessels. These did not show any ordered connection with the adjacent cystic parenchyma that appeared congested and with areas of hemorrhagic infarction. Notably, the arterial vessels of all basal segments apart from the posterior one were hypoplasic. Lymphatic endothelial cells (positive for D2-40) were widely present in the lung parenchyma and dilated lymphatic vessels were present not only in their typical location but also in the inter-alveolar septa. The cells lining

Fig. 1. Macroscopic sample of inferior right lobe. Note the entrance of the artery and its systemic branching in the congested posterior basal segment (a, b). The cut surface showed multiple cysts of varying diameters (c, d).

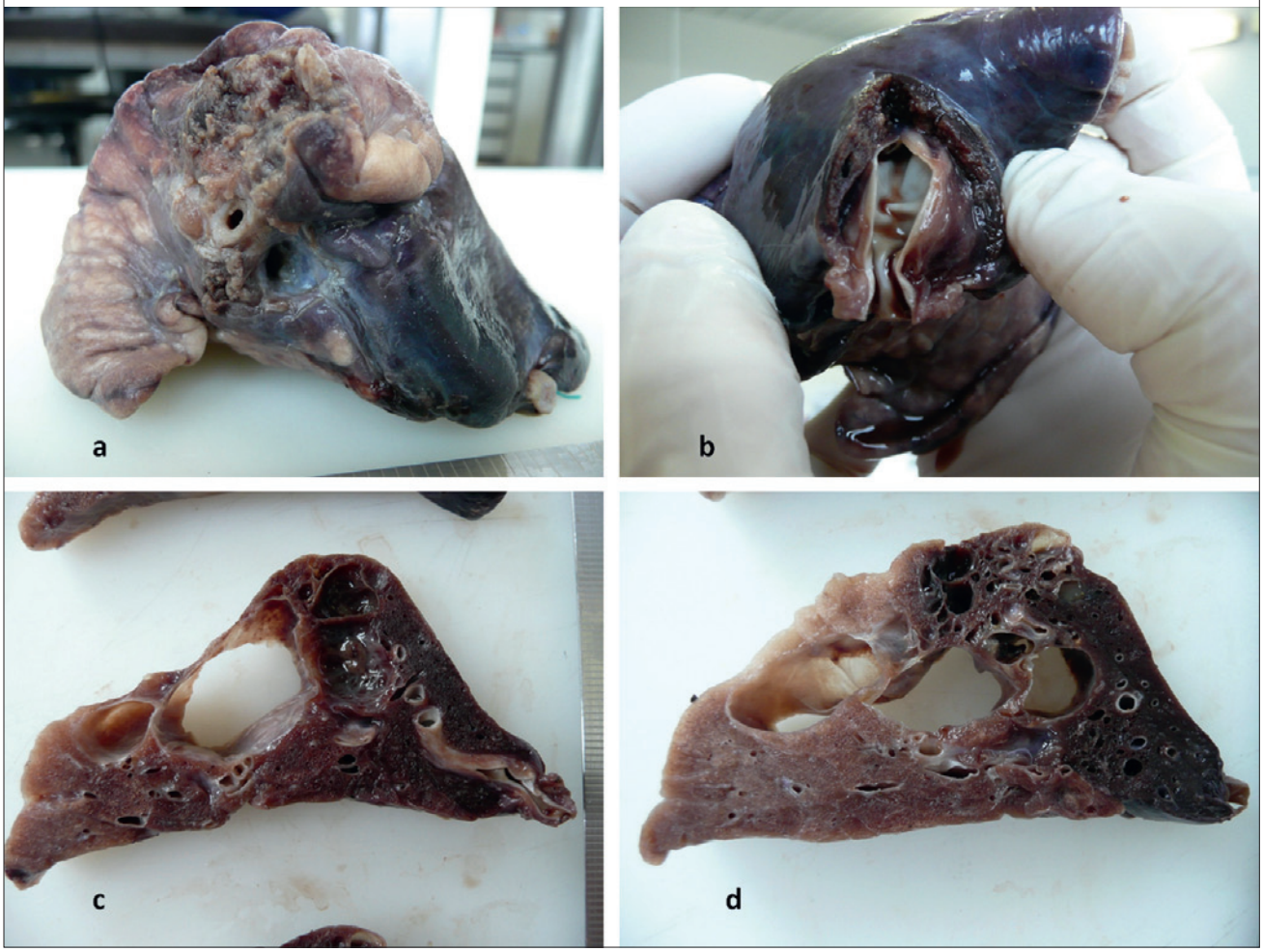
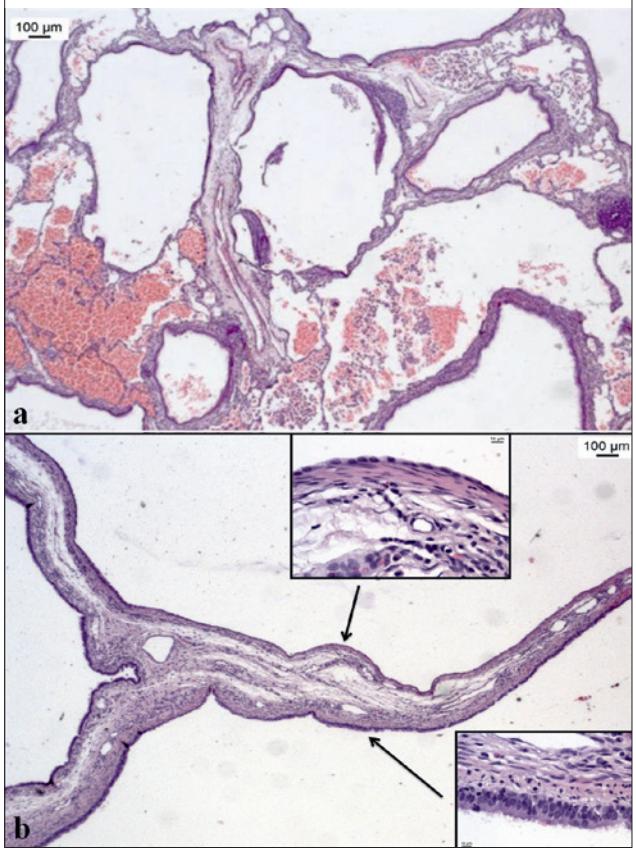


Fig. 2. Lung parenchyma at low magnification (HE). Note the numerous cysts of varying diameters (a). The cyst wall was formed by a central portion with blood and lymphatic vessels and an outer layer of smooth muscle. The epithelium lining was cubic or ciliated, without mucous cells (b).

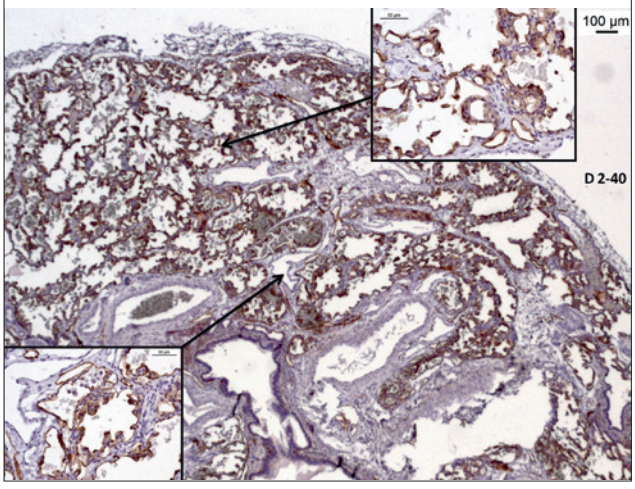


the cysts often showed the immunophenotype typical of bronchiolar epithelial cells, expressing for instance basal p63 and CK5 and apical TTF1 and CK7. Interestingly epithelial cells were also positive for D2-40 (Fig. 3).

Discussion

Cystic lesions are very frequent features in many congenital pulmonary abnormalities. However, the mechanism of their formation is still not clear [7] and the criteria used to classify cystic lesions such as CPAM are not well defined. Several studies report a high frequency of association (20 %) between CPAM and other congenital lesions, both CTMs and not-CTMs [8]. CPAM type 2 can be sometimes accompanied by bronchial atresia, EPS and, rarely, IPS [7 9 10]. The persistence of primitive bronchial arteries reaching the pulmonary buds before the development of pulmonary arteries is observed in most cases of IPS. Langston suggests that the presence of malformations such as cystic lesions of CPAM type could be responsible for the lack of physiological involution of embryonal vessels [4]. Lung buds are enveloped in a continuous mesenchymal surround throughout development. Blood vessels develop at the same time of airways within this mesenchymal component by capillary vasculogenesis that leads to the foregut-mesodermal pulmonary plexus. The latter needs a connection with the arterial system [11]. At first, this plexus is connected to the primitive branchial arteries. However, after the thirteenth week of embryonal life, it is reached by branches of the pulmonary arteries that have been developing by angiogenesis from the aortic sac. This event leads to the regression of the previously established systemic connections [12]. This complex process is under the direct control of molecular interactions between mesodermal and endodermal components regulating the lung development at different stages [11]. We have described a case of CTM associated with both vascular and airways lesions (IPS and CPAM type 2 respectively). The morphology of this rare malformation suggests the presence of an abnormal regulation of the interaction between mesoderm and endoderm that ultimately leads to the altered development of both components. The morphological aspects of CPAM type 2 may be a consequence of a defective and interrupted endodermal differentiation in the pseudo glandular phase. In fact, at the end of this stage, which lasts from the sixth to the sixteenth week of embryonal life, airways are completely formed and their branches reach the level of the acinus [13]. The impairment of the mesodermal component may have caused a defective development of the pulmonary plexus, the lack of connection between this and the pulmonary arterial system and the persistence of the one with the systemic circulation. This is supported by histological and radiological evidences of hypoplasia of the pulmonary arteries in the basal segments of the right inferior lobe. In addition, the abnormal expression of D2-40 (oncofetal protein M2A), documents the additional presence of an anomaly in the development of the lymphatic system [14]. This is in agreement with the hypothesis of a pathological mesodermal differentiation. Moreover, the persistence of this oncofetal protein in the

Fig. 3. Lung parenchyma at low magnification (D2-40). The oncofetal protein M2A was not only expressed in lymphatic endothelial cells, but also in epithelial cells. Note the abundance of lymphatic vessels which are dilated (inset). Negative controls was given by blood vessels.



epithelial cells suggests the endodermal component is also alterated [14]. In our case, the abnormal interaction between endodermal and mesodermal components of lung buds has happened at a specific time point, presumably around the thirteenth week of embryonal life, which corresponds to the pseudo glandular stage just before the establishment of connections between mesodermal plexus and pulmonary circulation. So, according also to the recently proposals for the classification of pulmonary malformations [1], CPAM would not be an hamartomatous lesion and the classification proposed by Stocker [3] based on the apparent "site of maldevelopment" might be incorrect. The right classification criteria may consider the time rather than the site of malformation. This new type of approach based on the temporal aspects of the endoderm/mesoderm interaction, suggested also by Clements et al [15], could lead to a more modern and correct classification of all types of CTMs.

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