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# Symptomatic pericardial cysts and dilemmas in their diagnosis

ADRIANA GRIGORAŞ[1,2)], CORNELIA AMĂLINEI[1,2)], IRINA-DRAGA CĂRUNTU[1)], CONSTANTIN CRISTIAN GRIGORAŞ[3)], IRINA RODICA CHISELIŢĂ[4)], RADU ADRIAN CRIŞAN-DABIJA[5)]

[1)]*Department of Morphofunctional Sciences I, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*

[2)]*Department of Histopathology, Institute of Legal Medicine, Iaşi, Romania*

[3)]*Specialty Ambulatory, Pneumology Clinical Hospital, Iaşi, Romania*

[4)]*Department of Pathology, Pneumology Clinical Hospital, Iaşi, Romania*

[5)]*Department of Internal Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*

## Abstract

Pericardial cysts (PCs) or pleuropericardial cysts are rare congenital mediastinal lesions with an approximate incidence of one in 100 000 persons. Usually, they are asymptomatic, being incidentally discovered during a routine chest imaging examination or an autopsy exam. The study involved a retrospective evaluation of clinicopathological findings in a 6-year series of PCs, treated in the Clinic of Pulmonary Diseases, Iaşi, Romania. A group of five cases of PCs, four females and one male, were evaluated. All patients displayed different symptoms, such as dyspnea, chest pain, chronic cough, fatigue, palpitation, and epigastric pain. The cystic lesions were located in the right and left cardiophrenic angle, in four cases, and in the central mediastinum in a single case. The lesions had a fluid content and a maximum diameter that ranged between 35 and 95 mm. The microscopic examination of the surgical resection tissues revealed a thin connective tissue wall without any associated smooth muscle cells. The loose connective tissue band was lined by a layer of mesothelial cells with no cellular atypia, which displayed discrete papillary projections, in one case. Although PCs are rare incidental findings, they should be considered in differential diagnoses of mediastinal cysts, especially as they are associated with non-specific symptoms. Furthermore, considering the possibility of development of severe complications, PCs should be thoroughly explored for suitable patients' management.

***Keywords***: pericardial cyst, mediastinum, congenital anomalies.

## Introduction

Pericardial cysts (PCs), also called pleuropericardial cysts, are rare lesions which comprise 7–18% of all the mediastinum benign masses and constitute about 33% of mediastinal cysts [1–3]. According to their morphology, localization, and content, PCs have been reported in the literature since the middle of 19th century with different terms, such as pleural cyst, mesothelial mediastinal cyst, para-pericardial cyst, pericardial coelomic cyst, simple cyst of the mediastinum, hydrocele of the mediastinum, PCs, spring-water or clear-water cyst, thin-walled cyst, and serosal cyst [1, 2, 4, 5]. Due to their predominantly anatomical location in the cardiophrenic angle, PCs are sometimes reported in the literature under the name of pleuropericardial cyst [3].

These are primarily congenital anomalies, with an estimated incidence of 1:100 000 persons, which occur because of the incomplete separation of the pericardial coelom after the third week of gestation [2, 6–8]. However, inflammatory cysts may also occur in the context of tuberculosis, echinococcosis, rheumatic pericarditis, trauma, including cardiothoracic surgery, or in patients on chronic hemodialysis, in exceptional cases [5, 9, 10].

More than 60% of PCs are diagnosed in the middle age [2, 8]. However, PCs have been reported in literature in all ages, from children up to 102 years old patients [8].

Typically disposed in the right anterior costophrenic angle, PCs are usually less than 5 cm in diameter, being mainly incidentally detected on routine chest images or during autopsy exams [11, 12]. Larger PCs are associated with different symptoms, according to their localization, such as chronic cough, chest pain, stridor, wheezing, dyspnea, retrosternal pressure, hemoptysis, fatigue, dysphagia, epigastric pain, tachycardia, palpitations, and cyanosis [5, 13, 14]. In rare cases, cardiac tamponade, atrial fibrillation, hiccups, intercostal neuralgia, superior vena cava syndrome, hoarseness, obstruction of the right main stem bronchus, hemidiaphragm paralysis, spontaneous pneumothorax, and right ventricular outflow tract obstruction, due to the adjacent structure's compression, have been reported [5, 8, 14, 15].

PCs display a unilocular feature, with a round or ellipsoid shape, and a clear fluid content. PCs' walls consist of mesothelium and a band of connective tissue, which mainly include collagen and few elastic fibers, without associated smooth muscle cells [2, 5]. The current management of PC

is based on the surgical removal of the lesion, especially in symptomatic cases. Although no malignant progression has been reported, the microscopic exam represents a significant step in PCs differential diagnosis from other benign or malignant mediastinal cystic lesions.

### Aim

Our study purpose was the evaluation the clinico-pathological features, along with differential diagnosis and management in PC miniseries of cases.

## Patients, Materials and Methods

The retrospective analysis included consecutive patients having PCs diagnosed in the Pneumology Clinical Hospital, Iaşi, Romania, during the last six years (June 2017–June 2023). Our database comprised clinicopathological data, along with chest radiography (X-ray), and computed tomography (CT) scan data reviewed from the clinical records of all cases.

Hematoxylin–Eosin (HE) and van Gieson trichrome stained slides of the surgical specimens were reviewed. Additionally, to improve the mesothelium identification, pan-cytokeratin (CK) AE1/AE3 and CK7 immuno-histochemistry (IHC) were performed. After xylene deparaffinization, the sections were progressively hydrated. Then, the slides were incubated overnight with the primary antibodies, after Epitope Retrieval Solution (pH 6, 96ºC, 20 minutes) treatment. After that, the slides were cooled at room temperature, washed with distilled water, and treated with hydrogen peroxide ($H_2O_2$), for 10 minutes, to inhibit the endogenous peroxidases. Primary antibodies specific for multi-CK AE1/AE3 (monoclonal antibody, mouse, code NCL-L-AE1/AE3-601, 1:100 dilution, Novocastra, UK) and CK7 (monoclonal antibody, mouse, code NCL-L-CK7-560, 1:100 dilution, Novocastra, UK) were applied. In the end, the immune reaction was visualized with 3,3'-Diaminobenzidine (DAB) chromogen solution, followed by a counterstain of the slides with diluted Hematoxylin. Positive external controls were used for the results control. The negative control was obtained by omission of the primary antibody.

The Research Ethics Committee of the Pneumology Clinical Hospital, Iaşi approved this research (Approval No. 104/10.07.2023), in alignment with the Declaration of Helsinki's principles regarding medical research involving human participants.

## Results

The study group included five patients diagnosed with PCs, four women and one man, all residents in urban areas. The patients' ages varied between 25 and 78 years old. The median patients' age was 58 years, and the mean was 56.4±18.72 years old. Upon admission, the patients displayed different symptoms, such as dyspnea, in all cases, followed, in a decreased order of frequency, by chest pain, in four cases, chronic cough, in three cases, fatigue, in two cases, and palpitation and epigastric pain, each in a case. Different comorbidities were identified in four cases, such as obesity, hypertension ± chronic ischemic heart disease, peptic ulcer, and cholelithiasis (Table 1).

**Table 1 –** ***The clinicopathological features of patients diagnosed with PCs, in the study group***

| Case # | Age [years] | Gender | Symptoms | Location (chest X-ray/CT) | Comorbidities | PCs size [mm] | Surgical approach | Follow-up [months] |
|---|---|---|---|---|---|---|---|---|
| 1. | 25 | F | Chest pain, dyspnea, fatigue | Right cardiophrenic angle | NA | 95/65 | Complete resection by right thoracotomy | 1/2 |
| 2. | 78 | F | Chronic cough, dyspnea, palpitation, chest pain | Central mediastinum | Hypertension ± chronic ischemic heart disease Obesity | 73/42 | Complete resection by right thoracotomy | 6 |
| 3. | 72 | M | Dyspnea, chronic cough, chest pain, epigastric pain | Left cardiophrenic angle | Hypertension peptic ulcer | 82/37 | Complete resection by left thoracotomy | 4 |
| 4. | 58 | F | Dyspnea fatigue | Right cardiophrenic angle | Hypertension cholelithiasis | 50/40 | Complete resection by right thoracotomy | 2 |
| 5. | 49 | F | Dyspnea, chronic cough, chest pain | Right cardiophrenic angle | Obesity | 35/30 | Complete resection by right thoracotomy | 3 |

CT: Computed tomography; F: Female; M: Male; NA: Not applicable; PC: Pericardial cyst; X-ray: Radiography.

The cystic lesions identified in chest X-ray and thorax CT scan were located in the right upper lobe in three cases, followed by left cardiophrenic angle and central mediastinum, each in one case (Figures 1–4). There were no mediastinal lymphadenopathies and anti-immunoglobulin G (IgG) antibodies for *Echinococcus* were negative in all cases. PCs were completely resected by right or left thoracotomy. No complications were registered after the surgical resection of the lesion.

The gross findings of surgical specimens revealed round-oblong, well-circumscribed cystic lesions with serous fluid content, and smooth internal surface, in all cases. The cystic lesions exhibited unilocular features in four cases, while a bilocular aspect was noted in one case. The PCs' maximum diameter has ranged from 35 to 95 mm.

The microscopic exam of the PCs' wall showed a single layer of flat or cuboidal cells, without cellular atypia, which were disposed on a band of loose connective tissue, rich in collagen fibers associated with few elastic fibers (Figures 5–9).

Foci of hemorrhage or discrete papillary projections and pseudoglands were detected, each in one case (Figures 10–12). No specialized epithelium, smooth muscle cells, areas of cartilage, or cholesterol granulomas were detected in the cysts' walls.

Intense cytoplasmic immunopositivity of pan-CK AE1/AE3 of the lining epithelial cells was registered in all cases (Figure 13, A and B). Additionally, a CK7 cytoplasmic positivity confirmed the mesothelial differentiation of the lining cyst epithelium, in all cases (Figure 14, A and B).

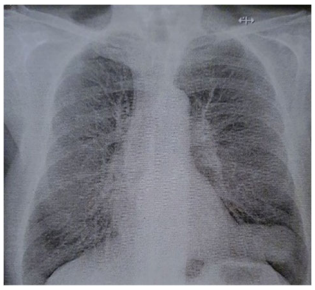

**Figure 1** – *An oblong, well-defined opacity disposed in the left para-cardiac area, abutting the lower left arch of the heart, which does not reach the chest wall (chest X-ray).*

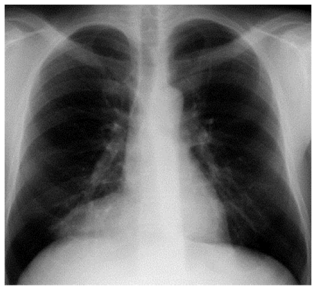

**Figure 2** – *A well-delimited ovoid opacity located in right cardiophrenic angle, in contact with the lower right arch of the heart (chest X-ray).*

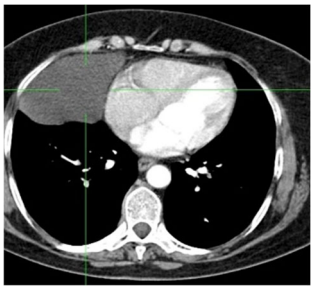

**Figure 3** – *An ovoid, sharply defined mass, with fluid density, without septation or solid component, located in the right cardiophrenic angle (non-contrast chest CT scan – axial image). CT: Computed tomography.*

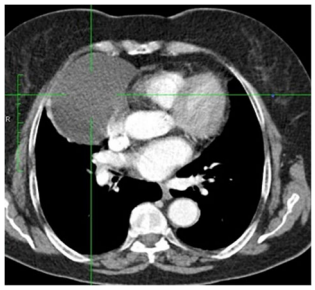

**Figure 4** – *Homogeneous mass with fluid density, located in the right cardiophrenic angle (non-contrast chest CT scan – axial image).*

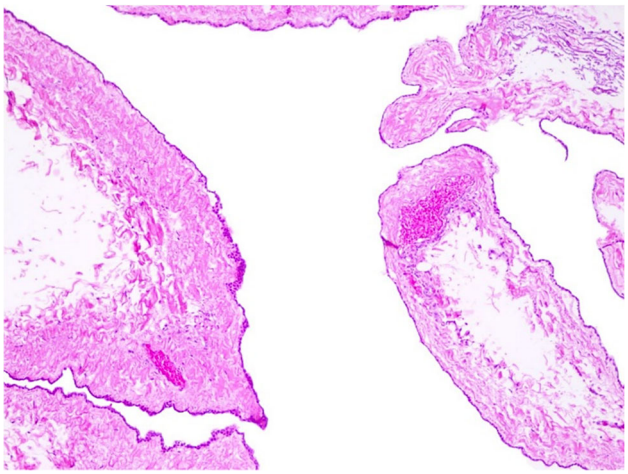

**Figure 5** – *General view of a PC specimen. HE staining, ×10. HE: Hematoxylin–Eosin; PC: Pericardial cyst.*

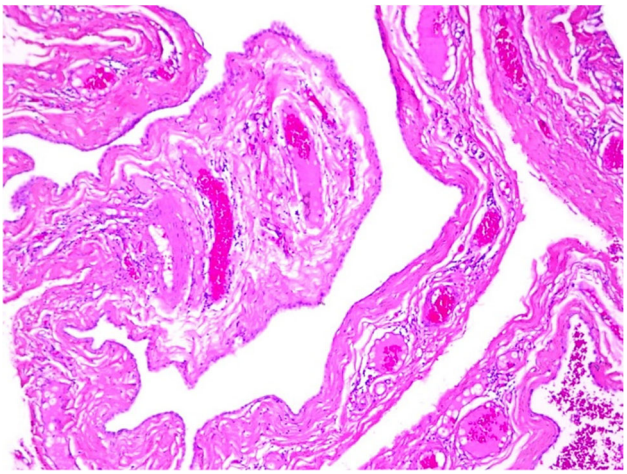

**Figure 6** – *General view of PC wall lined by a simple squamous to cuboidal epithelium. HE staining, ×10.*

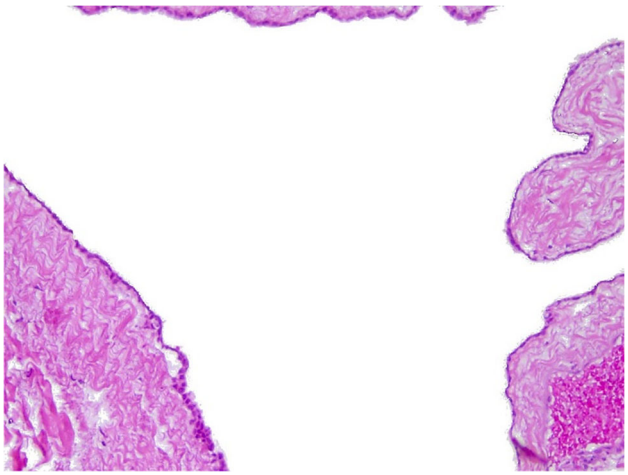

**Figure 7** – *PC wall consisting of connective tissue lined by a simple cuboidal epithelium. HE staining, ×20.*

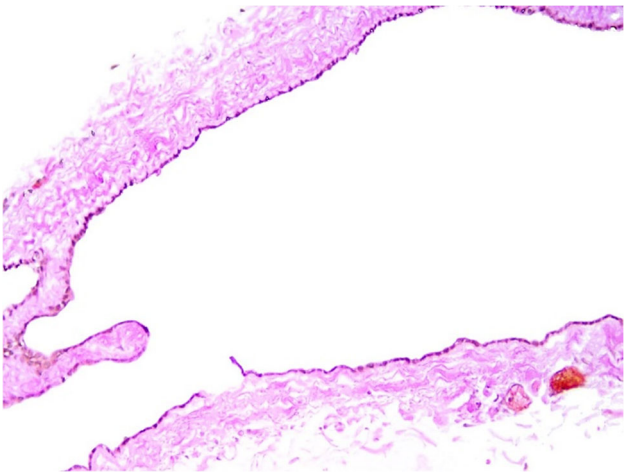

**Figure 8** – *Simple squamous epithelium in a PC wall. Van Gieson trichrome staining, ×20.*

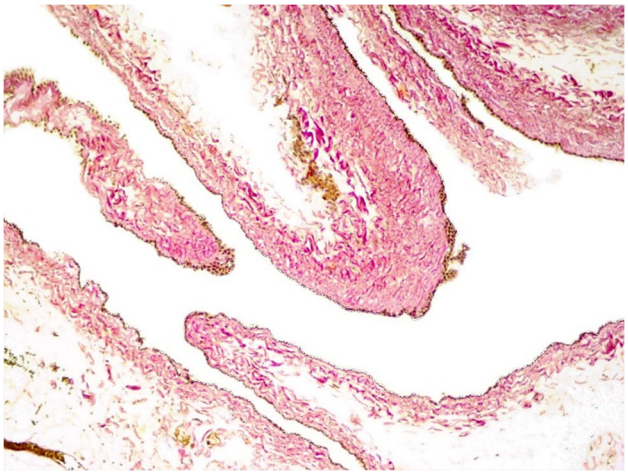

**Figure 9** – ***PC wall rich in collagen fibers. Van Gieson trichrome staining, ×10.***

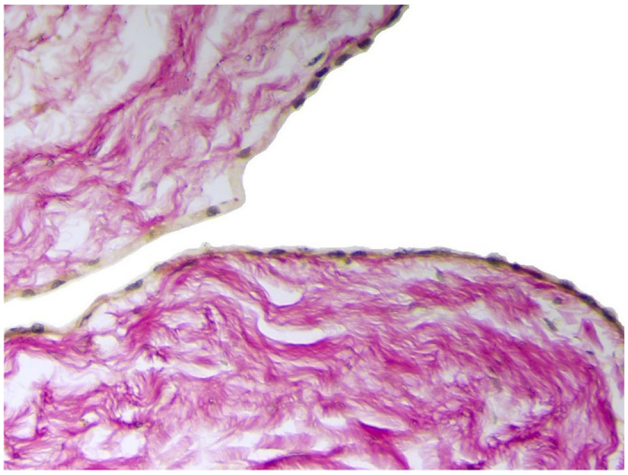

**Figure 10** – ***Numerous collagen fibers in a PC wall. Van Gieson trichrome staining, ×40.***

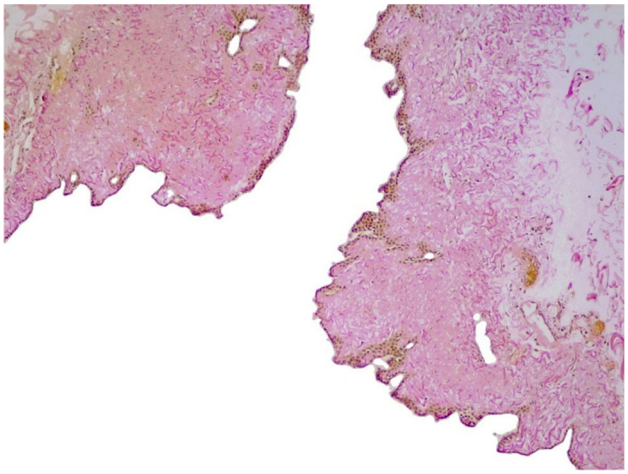

**Figure 11** – ***Discrete papillary projections and pseudo-glands in PC wall. Van Gieson trichrome staining, ×10.***

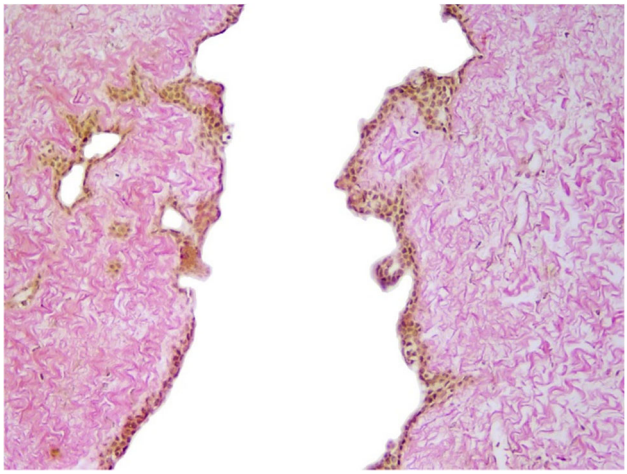

**Figure 12** – ***Detail of the previous figure showing pseudo-glands in the PC wall. Van Gieson trichrome staining, ×20.***

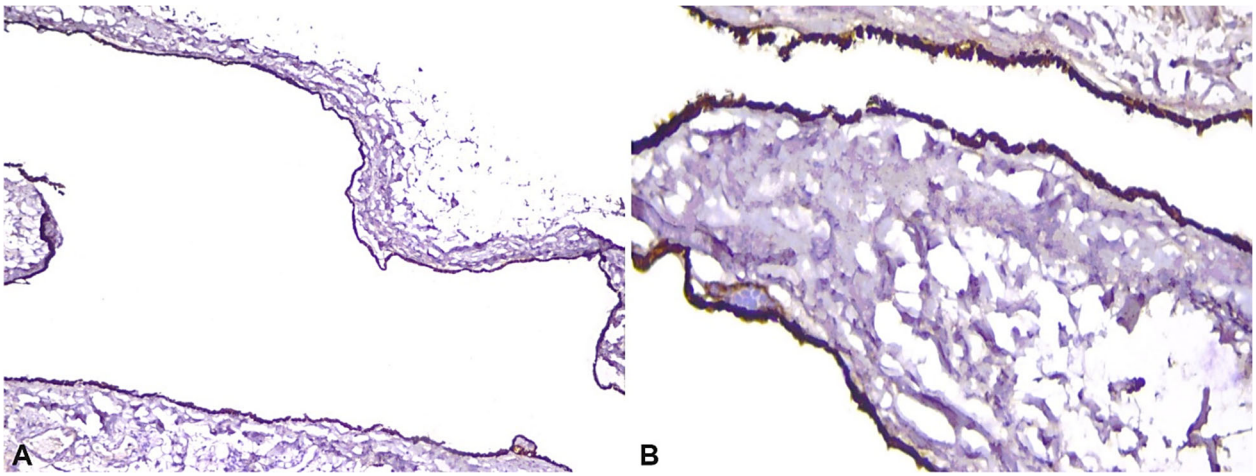


**Figure 13** – ***Pan-CK AE1/AE3 positive epithelial expression, in PC. Anti-pan-CK AE1/AE3 antibody immunomarking: (A) ×10; (B) ×20. CK: Cytokeratin.***

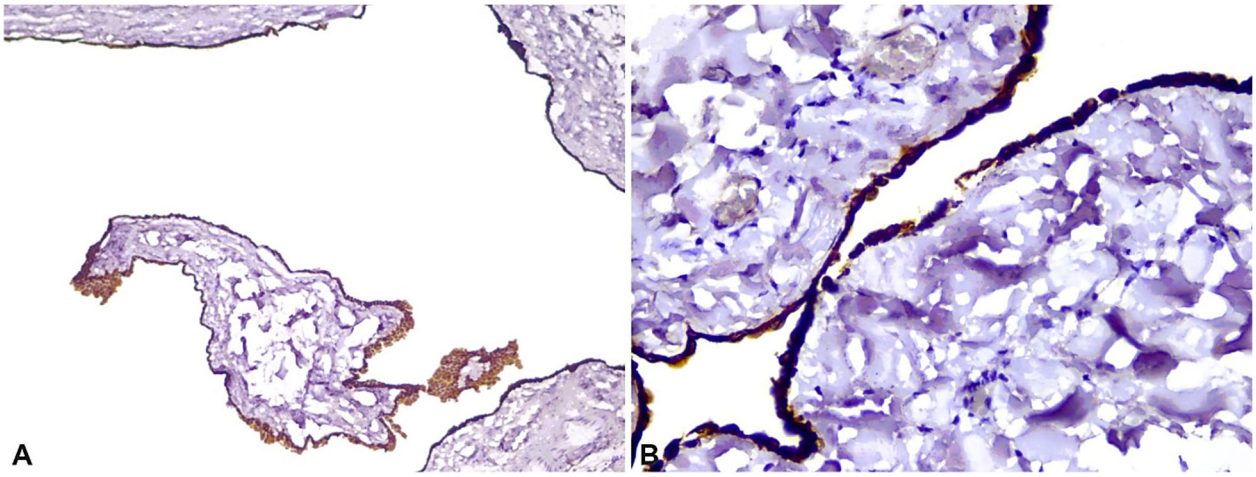


**Figure 14 –** ***CK7 positive epithelial expression, in PC. Anti-CK7 antibody immunomarking: (A) ×10; (B) ×40.***

## Discussions

PCs are rare mediastinal masses, commonly asymptomatic, incidentally diagnosed on routine chest radiographs. They occur because of an abnormal coelom division, early in embryogenesis [16]. Prenatal diagnosis in PCs is possible during an ultrasound examination, after the 14$^{th}$ week of gestation [17]. Congenital PCs and diverticula display similar developmental origin, the cystic lesions being considered a remnant of a diverticulum, while acquired inflammatory cysts occur due to a loculated pericardial effusion [1]. Moreover, different studies suggested that PCs are always connected with the pericardium, although a visible tube-like structure between them is described only in 5% of cases [8, 18].

PCs are usually diagnosed in the third or the fifth decade of life, although they were identified in patients of all ages [2], from a one-year-old boy [19] up to a 102-year-old woman [8]. Regarding gender, the female/male ratio in PCs varies among different reports from 1:1 [1] to 2:3 [20], 3:2 [5], and 8:4 [2, 21], partially due to the difficulty of large study groups set up. We found a median age of 58 years at the time of PCs diagnoses and a women's predominance (4/5 of cases), while the difference in the diagnosis age in our research, unlike the current literature data, is most probably related to the limited number of patients included in our study.

Predominately located in the right cardiophrenic angle (51–70% of cases), PCs have been additionally reported in the left cardiophrenic angle (22% of cases), followed by the anterior-superior and posterior part of the mediastinum (8% of cases) [1, 2]. These data agree with the results of another retrospective analysis performed on 101 PC cases from 139 publications, which revealed that PCs cystic lesions were mainly disposed in the right cardiophrenic angle, in 39.6% of cases, followed by the left cardiophrenic angle, in 18.9% of cases [5]. In rare cases, PCs have been described in other locations, including the subcarinal area, the right latero-tracheal region, and the left heart border [8]. Moreover, a pedunculated migrating PC, which can move around the chest cavity has been reported in an exceptional case [16]. In our study, in agreement with the literature data, PCs were mostly discovered in the right cardiophrenic angle, followed by the left cardiophrenic angle. In one case, the cyst was located in the central mediastinum, associated with the pulmonary arteries trunk and ascending aorta, which has represented an uncommon localization for PCs. Due to the limited incidence of these lesions, scarce literature data are available regarding PCs located in the central mediastinum, such as those in the right paratracheal space [22] or in the left and anterior area of the pulmonary artery [23].

Patients with PCs are usually asymptomatic (50–75% of cases), being incidentally detected in routine chest radiographs or thorax CT scans [1, 8, 24]. Larger PCs lead to symptoms including dyspnea, persistent cough, chest pain, fatigue, dysphagia, and cardiac arrhythmias, which appear in the context of compression of the nearby organs [2, 8]. Patients displayed similar symptoms, such as chronic cough, dyspnea, chest pain, palpitation, and fatigue, in our study group. However, it was a challenge to ascertain whether these clinical manifestations were associated with PCs, considering that three of the patients had various comorbidities, like hypertension with/without chronic ischemic heart disease, peptic ulcer, and cholelithiasis.

Although PCs are usually suspected in chest X-rays when an enlarged contour of the heart border is observed, thorax CT scan provides a more detailed description of the cystic lesion, regarding its size, structure, and anatomic location. In addition, in some cases, such as unusual location or higher protein content of the cyst fluid, magnetic resonance imaging allow PCs differentiation from hematomas or tumor lesions [1, 18]. Even if PCs have less than 50 mm in diameter when diagnosed on thorax images, large PCs up to 280 mm in diameter were also registered (Table 2) [25]. Generally, these cases are associated with uncommon symptoms, such as syncope, pneumonia, myocardial infarction, cardiac tamponade, congestive heart failure, or sudden death [1, 8, 24, 26]. PCs were also reported in association with other diseases, such as Fanconi anemia or ventricular septal defect and patent *ductus arteriosus*, in exceptional cases [5, 19]. Moreover, a recent study reports an unusual, calcified PC in a 50-year-old man, which possibly occurred in a chronic inflammation context [27].

PCs larger than 50 mm were noted in three cases from our study group, two located in the cardiophrenic angle and one in the central mediastinum, which could explain the related symptoms, considering their relationship with the pericardium, pulmonary arteries trunk, and ascending

aorta. Their maximum diameter varied from 73 to 95 mm, while the smallest lesion had 35 mm, our observations being comparable with other data reported in literature. In this context, a mean maximum diameter of 83 mm was noted by another recent study performed on 101 PC cases [5]. Moreover, according to the same study, the diameter of the cystic lesions varied between 15 and 170 mm in 42 out of 101 patients [5]. Similar results were observed by another research team, which revealed a maximum diameter of 95 to 100 mm in another miniseries of PC cases [37].

**Table 2 –** ***Specific features in normal pericardium and PCs***

| Features | Normal pericardium | | PC | | References |
|---|---|---|---|---|---|
| ***Development initiation*** | After the first week of gestation | | After the third week of gestation | | [2, 6–8] |
| ***Developmental regulatory genes*** | *BMP-2b/4*<br>*WT1*<br>*RALDH2*<br>*TBX 1/5*<br>*TBX 18* | | ? | | [28, 29] |
| ***Size*** | ≤2 mm | | 30–280 mm maximum diameter | | [2, 25, 30] |
| ***Pericardial space content*** | 15–50 mL of fluid, a plasma ultrafiltrate | | Up to1 liter of clear fluid | | [2, 30] |
| ***Structure*** | Visceral layer (epicardium) and parietal layer | | Thin cystic wall | | [2, 8] |
| ***Microscopy*** | Mesothelium and connective tissue | | Flat to cuboidal simple epithelium<br>Loose connective tissue<br>Foci of papillary hyperplasia | | [2, 5, 31] |
| ***Lining epithelium IHC profile*** | Positive | Calretinin<br>Podoplanin (D2-40)<br>Pan-CK AE1/AE3<br>CK CAM5.2<br>CK5/6<br>CK7<br>CK8<br>CK18/19 | Positive | Calretinin<br>Podoplanin (D2-40)<br>WT1<br>CK7<br>Pan-CK AE1/AE3 | [3, 32–35] |
| | Negative | CK14<br>p53<br>CD68<br>CD45<br>Ber-EP4<br>CK20<br>EMA<br>CEA<br>CA19-9<br>TTF-1<br>S100<br>CD34<br>NSE<br>CD56<br>MUC1/2/5AC/6 | Negative | ? | |
| ***Differential diagnosis*** | | | Bronchogenic cysts<br>Enteric/esophageal duplication cysts<br>Localized pleural/pericardial effusions<br>Thymic cysts<br>Morgagni hernia<br>Hiatal hernia<br>Pericardial cystic lymphangioma<br>Cystic teratoma | | [2, 5, 8] |
| ***Therapeutic management*** | | | Conservative follow-up<br>Percutaneous aspiration<br>Surgical cyst excision | | [5, 8] |
| ***Progress*** | | | No malignant transformation<br>Extremely rare recurrences | | [5, 8, 36] |

BMP: Bone morphogenetic protein; CA19-9: Carbohydrate antigen 19-9; CD: Cluster of differentiation; CEA: Carcinoembryonic antigen; CK: Cytokeratin; EMA: Epithelial membrane antigen; IHC: Immunohistochemistry; MUC: Mucin; NSE: Neuron-specific enolase; PC: Pericardial cyst; RALDH2: Retinaldehyde-specific dehydrogenase type 2; TBX: T-box transcription factor; TTF-1: Thyroid transcription factor-1; WT1: Wilms tumor 1 protein.

PCs may exhibit a multilocular feature [38] or foci of papillary hyperplasia [31], infrequently described in different reports. Likewise, a bilocular feature and discrete epithelial papillary projections were noted, each in a case of our study group. Moreover, pseudoglands in the cyst wall were registered due to the invagination of the epithelium into the connective tissue cyst wall, a feature not yet registered by other research teams.

Commonly, the diagnostic approach in PCs is based on chest imagistic results associated with the microscopic examination of the cyst wall.

Differential diagnosis of PCs includes a large spectrum of mediastinal cysts, starting from bronchogenic cysts, enteric/esophageal duplication cysts, localized pleural/pericardial effusion, thymic cysts, Morgagni hernia, hiatal hernia, cystic pericardial lymphangioma, and cystic teratoma (Table 2) [2, 5, 8]. Routine microscopic examination associated with trichrome special stains may confirm the diagnosis in these cases.

PCs do not have distinctive molecular features, but IHC markers, such as CKs (AE1/AE3, CK5/6, CK7), podoplanin (D2-40), calretinin, and Wilms tumor 1 (WT1) may be used

in selective cases to certify the mesothelial origin of the cyst lining epithelium [32–34, 39]. Smooth muscle actin (SMA) immunostaining may be used to certify the absence of smooth muscle cells in the PC walls. However, the use of trichrome stain has revealed the lack of a muscular component in the investigated cases from our study group.

Bronchogenic cysts are unilocular structures, lined by respiratory epithelium. These have a serous or mucinous material content and display smooth muscle cells, areas of hyaline cartilage or sero-mucous glands, variably associated with the cyst wall [40, 41]. Enteric/esophageal duplication cysts exhibit a unilocular feature, often have mucoid contents, and are lined by a variable or mixed epithelium, from simple squamous to simple columnar and pseudo-stratified columnar epithelium. A double layer of smooth muscle cells, some gastric glands, and no cartilage areas are observed in the cyst wall, features which are not characteristic for PCs [42].

The unilocular congenital thymic cyst shows a flattened epithelium and a thin wall which contains thymic tissue. Comparable with PCs, no cholesterol granulomas or inflammatory cells are observed in the congenital thymic cyst, while the thymic tissue associated with Hassall's corpuscles orientates the diagnosis [43].

Morgagni hernia and hiatal hernia are diaphragmatic hernia types mainly diagnosed on anterior-posterior and lateral chest radiographs or CT scans. These are associated with gastrointestinal and respiratory symptoms, like those observed in PC cases, but a multiphase CT scan may reveal the diaphragm and the organs that herniate through it [44].

Cystic lymphangioma consists of a collection of dilated lymphatic channels, which may be found in the pericardium, in exceptional cases. These exhibit a multilocular feature, the cystic spaces containing a watery to milky fluid. From a morphological point of view, cystic lymphangiomas comprise irregular vascular spaces with thickened walls, associated with lymphoid aggregates and smooth muscle cells in larger vessels. The vascular spaces are lined by a flattened endothelium, which expresses immunopositivity for cluster of differentiation (CD)31 and CD34, but is negative for calretinin, features that contribute to their differential diagnosis from PC [45, 46].

Skin with well-developed skin adnexa associated with other tissue/structures, including cartilage, bone, smooth or striated muscle cells, salivary and pancreatic gland tissue, gastrointestinal epithelium, adipose cells, and neuroglia, lines the cystic cavity of mediastinal teratomas [47]. All these features support their differential diagnosis [47].

The management of PCs can vary from conservative follow-up, percutaneous aspiration or surgical cyst excision by thoracotomy, sternotomy, or video-assisted thoracic surgery [8]. Although no particular recommendations are available regarding the period of time or the frequency of the follow-up, conservative treatment is usually applied in asymptomatic cases. Surgical excision is the "gold standard" therapeutic approach in symptomatic, complicated cases or atypical PC localizations, like that close to large vessels [5, 8]. The post-resection prognosis is excellent, as only one case of PC recurrence has been reported in literature [36]. The surgical excision of the cyst was the surgical choice in our study group, with excellent outcomes, according to the follow-up of the patients from our study group.

Our study provides significant data regarding the clinico-pathological features of PCs, considering their rare incidence and the limited number of cases series reported in literature.

## Conclusions

PCs are uncommon cystic lesions of the mediastinum, often detected as incidental findings during a routine chest X-ray or autopsy, mainly located in the right cardiophrenic angle. They may be associated with nonspecific symptoms, such as dyspnea, chronic cough, epigastric pain, or palpitation, that may lead to a delayed or an erroneous diagnosis.

The microscopic exam of the surgical resection samples confirms the PC diagnosis on chest X-ray suspected cases. Despite their simple structure, they may be associated with morphological particular features, such as papillary epithelial projections and pseudoglands, as were registered in our group. IHC markers may support the differential diagnosis from other cystic mediastinal lesions by certification of the mesothelial origin of the cyst lining epithelium.

Being well recognized that the surgery is the "gold standard" therapeutic approach in symptomatic, complicated or atypical PC localizations, the surgical excision of the cyst was the therapeutic choice in our study group, with excellent outcomes, according to the patients' follow-up.

Despite that PCs case series, such as that presented in our report, are rarely documented in literature considering their low incidence, their knowledge is important in clinical medical practice and in histopathological diagnosis.

### Conflict of interests

The authors declare that they have no conflict of interests.

### Authors' contribution

Adriana Grigoraş and Cornelia Amălinei equally contributed to this article.

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***Corresponding authors***

Cornelia Amălinei, Professor, MD, PhD, Department of Morphofunctional Sciences I, Grigore T. Popa University of Medicine and Pharmacy, 16 Universităţii Street, 700115 Iaşi, Romania; Phone +40740–072 376, e-mail: cornelia.amalinei@umfiasi.ro

Adriana Grigoraş, Associate Professor, MD, PhD, Department of Morphofunctional Sciences I, Grigore T. Popa University of Medicine and Pharmacy, 16 Universităţii Street, 700115 Iaşi, Romania; Phone +40740–170 027, e-mail: adriana.grigoras@umfiasi.ro, a_grigoras6600@yahoo.com

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