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# Posterior Mediastinal Paravertebral Müllerian cyst (cyst of Hattori): literature review

## Abstract

Mediastinal cysts are typically of bronchogenic, thymic or neurenteric origin, but may also represent oesophageal duplication. Posterior paravertebral mediastinal Müllerian cysts of undetermined pathogenesis are very rare occurrences. The first case of a ciliated cyst arising in the mediastinum, of probable Müllerian origin, was reported by Hattori in 2005, which gave rise to the name cyst of Hatorri (COH) The number of reported cases in literature of a similar nature have since then increased significantly. One of the main concerns about this pathology is the possibility of malignant transformation of the Müllerian tissue. Over the course of this paper we will discuss the pathogenesis, immunohistochemistry and its role in differential diagnosis as well as optimal treatment of such cysts.

**Key words:** Mullerian cyst, cyst of Hattori, posterior mediastinum, paired box gene 8

**Adv Respir Med. 2020; 88: 134–141**

## Introduction

The pathogenesis of Müllerian cysts, which are located in the posterior mediastinum, is not yet fully understood. It was suggested by Ludwig *et al.* in his study of Mayer-Rokitansky-Kuster-Hauser syndrome [1–3], that such cysts are possibly remnants of embryonic Müllerian tissue. The pathomorphology showed that the cysts were lined with ciliated columnar/tubal epithelium surrounded by a thin smooth muscular layer (Figure 1). The immunohistochemical profile demonstrated positivity to oestrogen as well as progesterone receptors. Such cysts, in relation to this condition, were first described by Hattori in 2005 as being female sex hormone receptor sensitive and situated in the posterior mediastinum [4].

## Pathogenesis

In 1998, Ludwig reported that "in stage 16 embryos, a thickening of the coelomic epithelium develops on the cranial end of the plica mesonephrica at the level of the 3$^{rd}$ to 5$^{th}$ thoracic vertebral blastema and forms the anlage of the funnel area (of the fallopian tube)" [1]. There is a possibility that some of the rudimentary tissue lined by fallopian tubal epithelium persisted in the paravertebral mediastinal areas at T4–6 levels [5]. Accordingly, a Müllerian cyst could develop anywhere along the path of Müllerian duct regression [3, 6]. However, the origin of these cysts is still not fully understood. Firstly, mediastinal structures are not regarded as part of the secondary Müllerian system. Secondly, embryonic Müllerian structures have not been identified in the mediastinum, pleura or pericardium [7].

In 2010, a paper discussing the pathogenesis of cyst of Hattori by Batt *et al.* suggested that the cyst originated from the primary Müllerian tissue similar to the postulated pathogenesis of Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH). This syndrome is characterized by the failure of the Müllerian duct to develop, resulting

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DOI: 10.5603/ARM.2020.0089
Received: 17.02.2020

ISSN 2451–4934

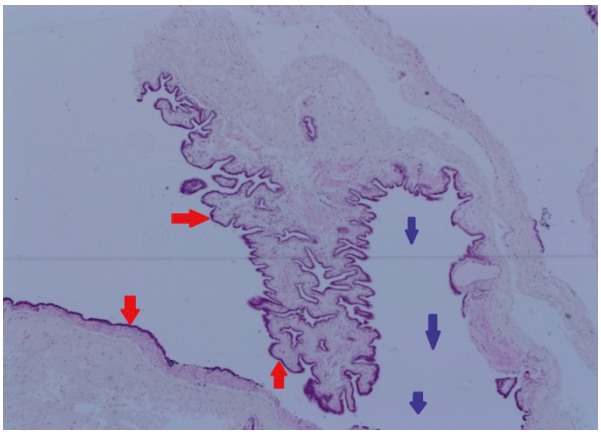

**Figure 1.** Haemotoxylin and eosin × 4, stained section of cyst of Hattori shows cystic spaces (blue arrows) with slightly fibrotic walls lined by ciliated columnar epithelium (red arrows)

in absence of the uterus and variable degrees of vaginal hypoplasia or agenesis [8]. Other theories include the notion that Müllerian cysts of Hattori may represent metaplastic changes of the mesothelium into ciliated epithelium [7].

## Clinical presentation

The most common sites of Müllerian cysts are within the pelvis [9], however, they can also be found, albeit less frequently, on the skin [10], the retroperitoneum or the mediastinum [11, 12]. Mediastinal cysts may present with chest symptoms, whereas abdominal cysts may present as an acute abdomen [13]. Mediastinal manifestations include cough (22%) [2, 9, 14, 15] chest pain (17%) [9, 16–18], shortness of breath [18], dysphagia [9], and arm numbness [18] (Table 1). However, amongst the 40 reported cases of COH, 55% were asymptomatic and detected as an incidental finding on imaging.

It is suggested that mediastinal cysts may account for up to 12–30% of mediastinal masses [19, 20] and Thomas-de-Montpréville at the Marie-Lannelong Surgical Centre in France, found that of a series of 163 cases of operated mediastinal non-malignant cysts, COH represented 5.5% of cases [21].

All reviewed cases of COH in literature are found in the female population, often amongst those with high body mass indexes, and in some instances associated with gynaecological pathology [3, 5, 9, 21, 22]. The presence of aromatase in fatty tissue may result in high levels of oestrogen, which could be a contributory factor in the development of COH [23]. Moreover, a possible association between COH and the use of hormone replacement therapy (HRT) has been reported in two cases [3, 5, 24]. Similarly to that of the female population, Müllerian cysts in men typically develop in the pelvis [25].

## Imaging

Cyst of Hatorri are often incidental findings of chest imaging [3, 5, 26–28]. Age of presentation are predominantly amongst woman between 40 to 60 years [22]. They are typically found between T3–T8 vertebrae [15] (Tables 1, 2); commonly occurring as a solitary cyst. However, multiple cysts have also been reported [2]. Imaging may detect an abnormality in a chest X-ray [18, 22], but computed tomography [24, 15, 17, 27] (Figure 2) or magnetic resonance imaging are recommended for detailed evaluation [15, 27] (Figure 3).

## Histology

Histologically, Müllerian cysts are lined with ciliated columnar/tubal epithelium, surrounded by a thin smooth muscular layer without atypia or mitosis. Whilst this is identical to the histology of the fallopian tube (Figure 1), differential diagnoses should include mesothelial, gastro-enteric, thoracic duct or pericardial cysts [5, 9, 26] (Table 3).

## Immunohistochemistry

The immunohistochemistry of COH shows positive expression for oestrogen (Figure 4) and progesterone receptors (Figure 5) [2, 11, 14, 15, 21, 22, 24]. The hormone receptor expression in the cyst wall, as well as the histological similarity to fallopian tube, supports the theory of its origin being remnants of embryonic Müllerian tissue [26]. This is further reinforced by the fact that the immunohistochemical profile of retroperitoneal Mullerian cysts are indistinguishable from that of the paravertebral mediastinal cysts [11]. Furthermore, all known reported cases in literature have been found within the female population [2, 3, 4, 9, 11, 15, 16, 18, 19, 21, 22, 24, 26, 28].

Cytokeratin 7 (CK7) is type II keratin of simple non-keratinizing epithelia which is present in uterine tubal epithelium as well as COH [11, 22, 27]. It has shown expression in our case, however, CK7 is not a specific marker as it has shown positivity in carcinoid [29] as well. Furthermore, pan-Cytokeratins (CK AE1/AE3) has also been detected in the COH [20, 24].

**Table 1. Müllerian cyst of Hattori presentation, size and hormonal status in 40 cases reported in literature**

| Author/year | Age/sex | Clinical symptoms | Paravertebral level | Diameter | ER/PR | CK7 | WT1 | Paired Box Gene 8 (PAX8) |
|---|---|---|---|---|---|---|---|---|
| **Hattori 2005** | 52/F | Persistent cough | Right T6 | 2.5 cm | +/+ | | | |
| | 18/F | Incidental | Right T5 | 2.0 cm | +/+ | | | |
| | 49/F | Cough | Left T4 | 2.0 cm | +/+ | | | |
| **Thomas-de-Montepreville 2007** | 40/F | Chest pain | Left T4 | 1.5 cm | +/+ | | | |
| | 46/F | Cough | Left T4 | 3.3 cm | +/+ | | | |
| | 47/F | Cough | Right T4/5 | 5.0 cm | +/+ | | | |
| | 48/F | Incidental | Left T5 | 3.0 cm | +/+ | | | |
| | 50/F | Chest pain | Right T3/4 | 3.2 cm | +/+ | | | |
| | 51/F | Incidental | Left T3/4 | 3.0 cm | +/+ | | | |
| | 56/F | Incidental | Left T8 | 1.3 cm | -/+ | | | |
| | 58/F | Cough | Pre-vertebral T5 | 4.5 cm | -/- | | | |
| | 59/F | Chest pain | Right T2–4 | 2.5 cm | -/- | | | |
| **Businger 2007** | 54/F | Incidental | Left T4–6 | 4.5 cm | +/+ | | | |
| **Batt 2010** | 41/F | Chest pain | Left T6 | 2.1 cm | +/+ | | | |
| **Kobayashi 2012** | 53/F | Incidental | Right T5 | 2.0 cm | +/+ | | | |
| **Liao 2012** | 48/F | Chest tightness | Right T7 | 5.1 cm | +/+ | | | |
| **Simmons 2013** | 52/F | Shortness of breath | Pre-vertebral T4 | 4.1 cm | +/+ | | | |
| | 47/F | Incidental | N/A | 5.0 cm | +/ | | | |
| **Lee 2014** | 42/F | Incidental | Right T6 | 2.6 cm | +/+ | | | |
| **Miyawaki 2014** | 51/F | Incidental | Left T5/6 | 4.0 cm | +/+ | | | |
| **Takahashi 2014** | 47/f | Incidental | Right T4/5 | 2.0 cm | +/+ | + | | |
| **Chon 2015** | 51/F | Chest pain | Left T6 | 3.0 cm | +/+ | | | |
| **Dakak 2015** | 51/F | Dysphagia | Pre-vertebral T5 | 2.7 cm | +/+ | | | |
| **Skancke 2015** | 35/F | Cough | Bilateral | 8.0 cm 4.0 cm | +/+ | | | |
| **Lochowski 2017** | 53/F | Incidental | Right T4 | 3.0 cm | +/+ | | | |
| **Tsai 2017** | 44/F | Incidental | Left T4 | 1.2 cm | +/+ | + | | |
| **Chandra 2017** | 52/F | Chest pain/SOB | Left T3–5 | 3.9 cm | | | | |
| **Mowad 2017** | 49/F | Cough | Left T4 | 3.6 cm | +/+ | + | + | + |
| **Karpathiou 2017** | 51/F | Incidental | Left T4 | 3.0 cm | +/+ | + | + | |
| **Oshima 2017** | 48/F | Incidental | Left T4–5 | 3.1 cm | +/+ | | | |
| | 40/F | Incidental | Right T3–4 | 3.5 cm | +/? | | | |
| **Lee 2018** | 22/F | Incidental | Left T10 | 2.4 cm | +/+ | | + | |
| **Chao 2018** | 49/F | Incidental | Right T5 | 1.3 cm | +/+ | + | | + |
| **Miura 2018** | 50/F | Cough | Left T6–7 | 1.9 cm | +/+ | | | |
| | 52/F | Incidental | Right T3–4 | 5.2 cm | +/+ | | | |
| | 46/F | Incidental | Right T4–5 | 4.1 cm | +/+ | | | |
| | 52/F | Incidental | Left T1–2 | 3 cm | +/+ | | | |
| **Sekimura 2018** | 40/F | Incidental | Left | 1.2 cm | +/+ | | | + |
| **Idaewor 2018** | 56/F | Cough | Left T3–4 | 3 cm | +/+ | | | |
| **Adachi 2018** | 53/F | Incidental | Right T5 | 3 cm | +/+ | | | + |
| **Yasukawa 2018** | 41/F | Incidental | Pre-vertebral T10 | 3 cm | +/+ | + | | + |

**Table 2. Clinical picture in the 40 COH reported cases**

| Clinical characteristics | N = 40 |
|---|---|
| **Age** | Average (18–59) |
| **Sex** | |
| F | 40 |
| M | 0 |
| **Size (cm)** | Average (1.2–8.0) |
| **Lateralisation** | |
| Right | 15 |
| Left | 20 |
| Pre-vertebral | 3 |
| Bilateral | 1 |
| N/A | 1 |
| **Vertebral level** | |
| T2 | 1 |
| T3 | 5 |
| T4 | 12 |
| T5 | 8 |
| T6 | 5 |
| T7 | 1 |
| T8 | 1 |
| T9 | 0 |
| T10 | 1 |
| Multiple | 3 |
| N/A | 3 |
| **Symptoms** | |
| Asymptomatic | 22 |
| Cough | 9 |
| Shortness of breath | 1 |
| Chest pain | 7 |
| Dysphagia | 1 |
| **Immunohistochemistry** | |
| ER+ | 36 |
| ER- | 3 |
| ER N/A | 1 |
| PR+ | 35 |
| PR- | 2 |
| PR N/A | 3 |
| PAX8+ | 4 |
| PAX8 N/A | 36 |

ER — oestrogen receptors; PR — progesterone receptors; PAX8 — paired box gene 8

Wilms' tumor protein 1 (WT1) is transcriptional regulator protein that is thought to inhibit transcription of growth promoting genes. This protein is expressed in tissue of the fallopian tube as well as the Müllerian system [30] and in COH [2, 15].

Paired box gene 8 (PAX-8); a gene found at 2p13, is associated with tumours of thyroid gland, kidney/upper urinary tract and Müllerian system [30, 31] and is positive in COH [2, 15, 22, 25, 27]. Cancer antigen 125 (CA-125), a protein encoded by MUC16 gene, is used as a tumour marker with a 79% sensitive for ovarian cancer. As it is present in amnion, coelomic and Müllerian epithelium [32–34], it has been found to be useful in the diagnosis of COH [2, 11] (Figure 6). Cytokeratin 5/6, specific for mesothelial differentiation and usually positive in squamous epithelia, myoepithelial cells, and mesothelial cells, are negative in COH [21].

Cytokeratin 20(CK20), an epithelial marker often used to distinguish colon carcinoma (80% are CK20+) [35], shows positivity in Merkel cell carcinoma and is positive only in some cases of extra-pulmonary small cell lung carcinoma [29]. Müllerian cysts show immunonegativity for CK 20 [11, 36].

Calretinin, a calcium binding protein, is positive in epithelioid pleural mesothelioma [40] but is negative in COH [7, 11, 22, 27] (Figure 7).

Thyroid transcription factor (TTF-1), also called thyroid specific enhancer binding protein, distinguishes primary lung (TTF1+) from metastatic (usually TTF1-) lung carcinoma [37]; it is negative in Müllerian cysts [15, 17, 19].

BerEP4 marker, also known as epithelial cell adhesion molecule, is an antibody to cell

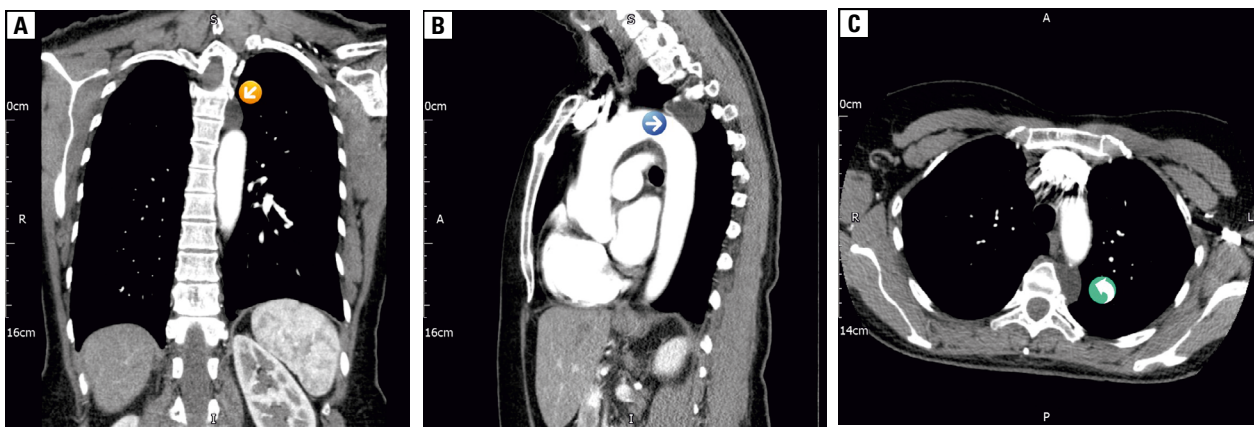


**Figure 2. A.** Chest computed tomography (CT) coronal view; soft tissue mass at the level of aortic arch (orange arrow); **B.** CT chest-sagittal view; soft tissue mass at the level of aortic arch (blue arrow); **C.** CT chest-axial view; soft tissue mass at the level of aortic arch (green arrow)

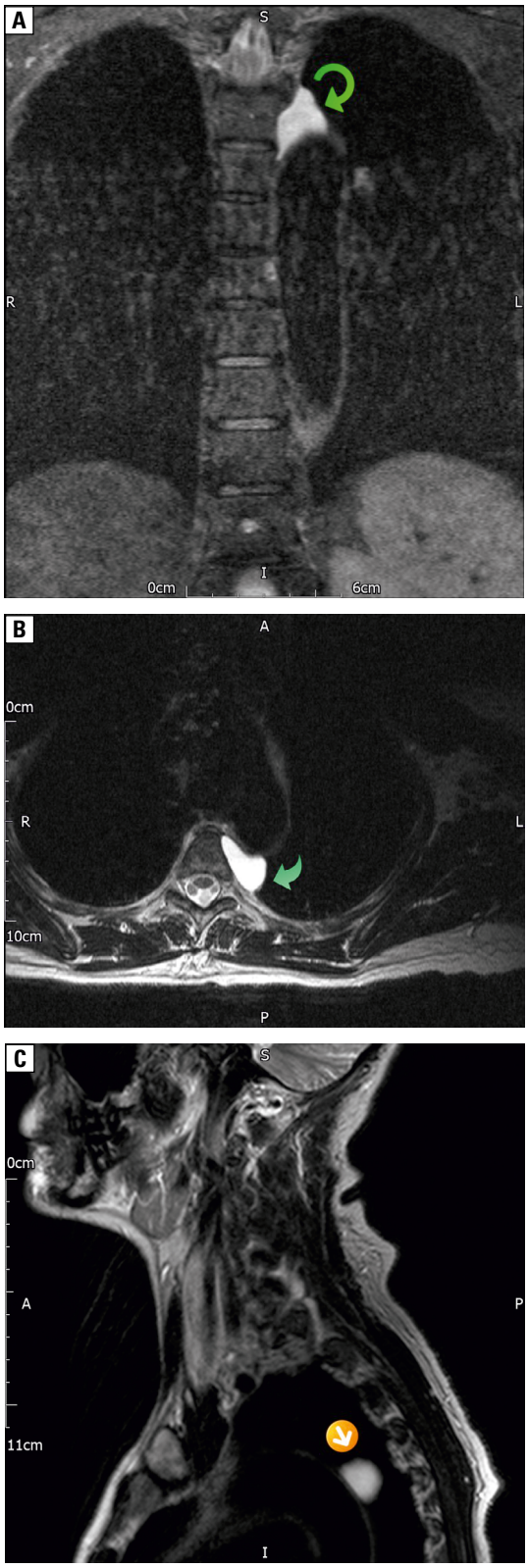


**Figure 3. A.** Magnetic resonance image (MRI) chest-coronal view; left paravertebral mass of cystic nature seen very close to the aortic arch (green arrow); **B.** MRI chest-axial view; left paravertebral mass of cystic nature seen very close to the aortic arch (green arrow); **C.** MRI chest-sagittal view; left paravertebral mass of cystic nature seen very close to the aortic arch (orange arrow)

**Table 3. Histopathology of the mediastinal cysts [5, 9, 14, 39, 41]**

| Origin | Histology |
|---|---|
| Mullarian (Hattori) | Ciliated columnar/tubal apocrine-like secretory cells, surrounded by smooth muscles. They are Oestrogen Receptor and progesterone receptor positive (ER+/PR+) |
| Bronchogenic | Pseudostratified, ciliated columnar epithelium, smooth muscles, cartilage and bronchial gland |
| Enterogenous | Gastrointestinal mucosa |
| Mesothelial | Single-cell layer of mesothelial cells surrounded by external fibrous capsule |
| Neurenteric | Enteric and neural tissue |
| Pericardial cysts | Single layer of mesothelial cells |
| Thoracic duct cysts | Lymphatic duct lining |
| Thymic cyst | Flattened cuboidal epithelium and Hassal's corpuscles |
| Hydatid cyst | Germinal layer with nucleoli . Protoscolices with double row hooklets round suckers that comprise "hydatid sand". Daughter cysts |

ER — oestrogen receptors; PR — progesterone receptors

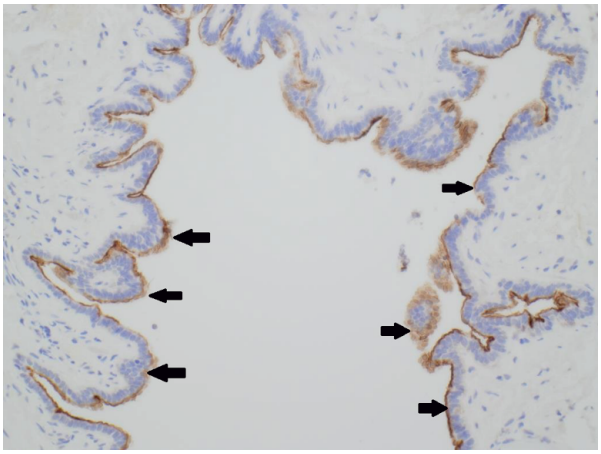

**Figure 4.** ×10, the lining epithelial cells are strongly positive for oestrogen receptors (arrows)

membrane glycoprotein expressed on healthy epithelia and in various carcinomas. This marker is reported to be negative in mesotheliomas [38]. Conversely, BerEP4 is reported to be positive in COH [7] (Figure 8).

Thrombomodulin, a transmembrane glycoprotein and cofactor for the thrombin-mediated activation of protein C, has a 95% specificity and 65% sensitivity to mesothelioma [39]. This marker is negative in COH [7] (Figure 9).

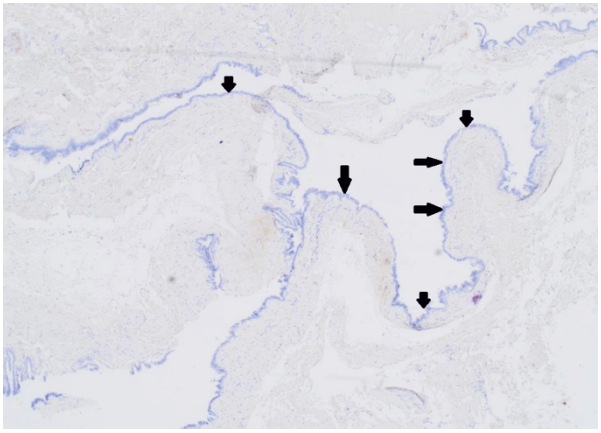

**Figure 5.** ×10, the cells are also strongly positive for progesterone receptors (arrows)

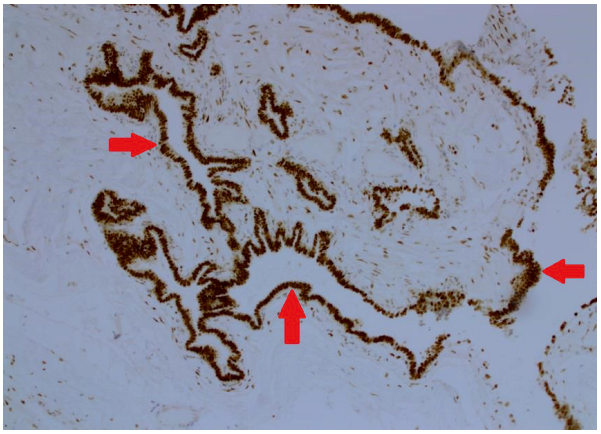

**Figure 8.** ×10, the epithelial cells are strongly positive for BerEP4 (arrows)

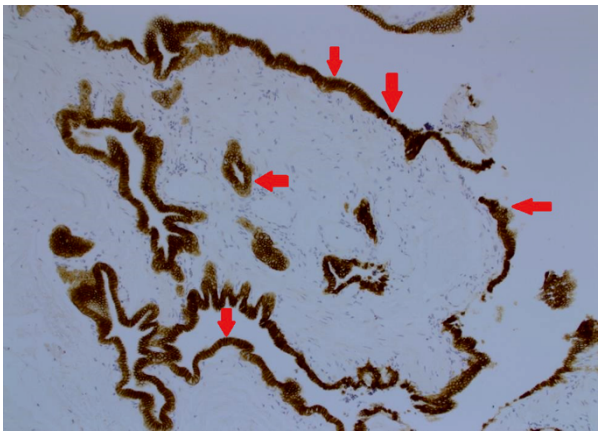

**Figure 6.** ×10, there is weak luminal staining of the epithelial cell with cancer antigen 125

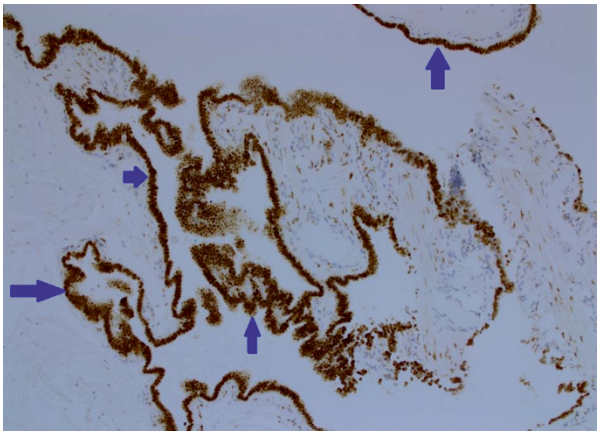

**Figure 9.** ×10, the epithelia cells are negative for Thrombomodulin (arrows)

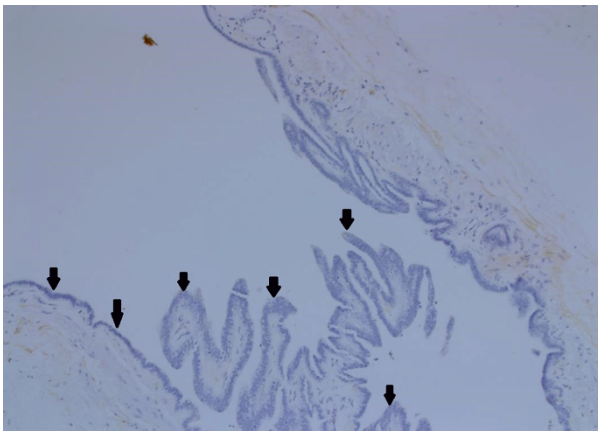

**Figure 7.** ×10, the epithelial cells are negative for Calretinin (arrows)

## Differential diagnosis

Generally, mediastinal cysts are rare; they can be either acquired or congenital and their origins may be of Müllerian, thymic [40], pericardial, bronchogenic or neuroenteric tissue. They may also represent oesophageal duplication [18, 28]. Other differential diagnoses may include mesothelial, gastro-enteric, thoracic duct cysts [26] or due hydatid disease [41] (Table 3). Anterior spinal meningocele containing cerebrospinal fluid, located in the posterior mediastinum, may appear as a cystic lesion, however, a meningocele will communicate with the spinal canal unlike a true cyst [3].

## Treatment

The long-term prognosis of Müllerian cysts is unclear. However, the risk of malignant transformation must not be discounted. The evidence suggests that presence of embryonic tissue away from its typical site, may give rise to malignant transformation. For example, cryptorchidism

within the male population significantly increases the risk of developing testicular cancer. Furthermore, patients with mediastinal goitres are more susceptible to thyroid cancer. Surgical excision is advisable to ensure formal analysis and diagnosis, symptomatic relief and elimination of possible malignant transformation of the Müllerian tissue [18, 42]. Surgical approaches taken include open thoracotomy [7, 9] or video-assisted thoracoscopic surgery (VATS) [3, 15, 25, 27, 43–45].

## Conclusion

Of all reviewed cases in literature, COH are found with the female population; often amongst those with high BMI's and in conjunction with gynaecological pathology. Histological appearance shows ciliated columnar epithelium surrounded by a smooth muscular layer, identical to the histology of the fallopian tube, supporting the theory of probable Müllerian origin. Surgical excision of such cysts are the treatment of choice as this allows for definitive diagnosis, symptomatic relief and a reduced risk of malignant transformation of Müllerian tissue.

## Acknowledgment

Authors would like to thank Ms Sarah Colquhoun, Senior Library Assistant at Basildon Healthcare Library at Basildon University Hospital for her valuable assistance in collecting the scientific reference papers.

## Conflict of interest

None declared.

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