

## A Case Report and a Short Literature Review of Pulmonary Sequestration Showing Elevated Serum Levels of Carbohydrate Antigen 19-9

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Pulmonary sequestration is a type of bronchopulmonary malformation defined as an isolated portion of lung tissue with systemic arterial supply and no bronchial communication. Carbohydrate antigen 19-9 (CA19-9) has been used for diagnosis and follow-up of gastrointestinal tumors. The current study presents a rare case of intralobar pulmonary sequestration associated with the marked elevation of CA19-9. A 39-year-old female patient was admitted to our hospital due to acute liver injury with marked elevation of serum CA19-9 (3,051.1  $\mu\text{mol/mL}$ ), and was then diagnosed with intralobar pulmonary sequestration after examination and surgery. After the pulmonary resection, the serum CA19-9 levels decreased to normal ranges. We briefly reviewed the literature on elevated serum CA19-9 levels and pulmonary sequestration since 1988. We found that serum CA19-9 levels are increased not only in patients with digestive tract cancers but also in those with nonmalignant diseases such as pulmonary sequestration.

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**Key words:** pulmonary sequestration, carbohydrate antigen 19-9, digestive tract cancers

### Background

Pulmonary sequestration is a rare congenital abnormality characterized by the presence of lung tissues that are not attached to the pulmonary arterial blood architecture but receive blood supply from an anomalous systemic artery<sup>1</sup>. As a result, sequestered lung tissues fail to function in or contribute to respiration. In 1946, Pryce first dubbed the condition “pulmonary sequestration,” which can be divided into two types according to the morphology: intralobar and extralobar<sup>2</sup>. Intralobar pulmonary sequestration is typically located in the posterior basilar segment of the lower lobe sharing a common visceral pleura. It accounts for 75 percent of all sequestrations and is usually diagnosed in early childhood with symptoms of recurrent infections, hemoptysis, or pleural effusion. The extralobar variety accounts for 25% of cases. The anomalous tissue is isolated from normal lung tissue with its own pleural envelope and may be located in the pericardium, in the mediastinum, as well as below the

diaphragm<sup>3</sup>.

Carbohydrate antigen 19-9 (CA19-9) was first identified by Koprowski in 1979<sup>4</sup> and is an important and well recognized tumor marker for pancreatobiliary and gastrointestinal tract cancer. In addition, recent clinical investigations have revealed that CA19-9 levels can also be elevated in other gastrointestinal tract disorders such as benign pancreatic, liver and biliary tract diseases<sup>5,6</sup>, and in respiratory diseases such as idiopathic interstitial pneumonia, collagen disease-associated pulmonary fibrosis, diffuse panbronchiolitis, and lung cancer. Therefore, the CA19-9 is not a specific marker for gastrointestinal, pancreatic and biliary malignancies<sup>7,8</sup>.

There has been a growing interest in investigating the relationship between pulmonary sequestration and elevated CA19-9 since Shiota et al. first reported a case of increased levels of CA19-9 in pulmonary sequestration in 1988<sup>9</sup>. Since then, numerous investigations, mostly from Japan, have reported cases of pulmonary sequestration

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Table 1 Laboratory data obtained on admission

Hematology	WBC	4.7×10 <sup>9</sup> /L	Virology	Anti-HCV	negative
	Hb	132 g/L		Anti-HIV	negative
	RBC	3.81×10 <sup>9</sup> /L		HBsAg	negative
	PLT	347×10 <sup>9</sup> /L ↑		HBsAb	positive
Biochemistry			Tumor markers	HBeAg	negative
	ALT	2,563 U/L ↑		HBeAb	positive
	AST	1,139 U/L ↑		HBcAb	positive
	TBIL	94 U/L ↑		CEA	3.3 µg/L (NV<5.0)
	TP	64.1 g/L		CA125	32.8 U/mL (NV<35.0)
	BUN	2.3 mmol/L ↓		CA19-9	3,051.1 U/mL ↑ (NV<37.0)
	Cr	44 µmol/L		CA153	14.2 U/mL (NV<31.0)
	Na	140 mmol/L		AFP	2.7 ug/L (NV<20.0)
	K	4.34 mmol/L			
	Cl	102 mmol/L			
	Serology	IgG		10.7 g/L	
IgA		5.79 g/L			
IgM		1.19 g/L			
Complement C3		1.4 g/L			
Complement C4		0.36 g/L			
ANA		negative			
ASMA		negative			
AMA		negative			

↑ abnormally high, ↓ abnormally low, NV normal value

and elevated CA19-9. We present a new case of pulmonary sequestration and elevated CA19-9 and have reviewed all reports related to pulmonary sequestration and elevated serum CA19-9 levels since it was first reported in the literature.

### Case Report Presentation

A 39-year-old woman was referred to our hospital with complaints of fatigue and weakness. Physical examination was normal except for yellowing of the sclera and skin. Laboratory examinations on admission showed significant increases in serum alanine aminotransferase (2,563 U/L), aspartate aminotransferase (1,139 U/L), total bilirubin (94 µmol/L) and CA19-9 (3,051.1 µ/mL) (Table 1). An initial diagnosis of acute icteric hepatitis was made. However, the etiologies of hepatitis such as viral infection, alcohol and hepato-toxic drugs intake, nonalcoholic steatosis, autoimmune disease, and biliary tract diseases were excluded. The cause of acute hepatitis remained unclear until the patient was discharged from hospital. During the patient's stay in hospital, we tried to determine why there was a significantly elevated levels of CA19-9. To exclude the possibility of underlying digestive tract malignancies, the patient underwent esophagogastroduodenoscopy, colonoscopy, and chest

and abdominal computer tomography (CT). No abnormal malignant lesions were found in the digestive tract, but computer tomography of the chest showed a 27×40 mm heterogeneous low density mass located in the left lower lobe close to the paravertebral sulcus (Fig. 1). To further identify this lesion, contrast-enhanced computer tomography was performed, and the results showed two fluid density shadows in the lesion and a suspicious funicular vessel arising from the upper edge of the aorta and coursing into the lesion. The presence of an aberrant artery arising from the superior border of the aorta was confirmed after surgery. Hence, the initial diagnosis of pulmonary sequestration was made. A left lower lobectomy was performed and histological examination of the resected tissue revealed chronic mucopurulent inflammation of the bronchial mucosa and lung tissue, as well as micro abscess formation in the focal area, signs which are consistent with the histology of pulmonary sequestration (Fig. 1).

There were no significant events in the postoperative course. Ten days after the excision of the tissue, the serum CA19-9 levels dramatically declined to 756 U/mL and returned to the normal value after 6 months (Fig. 2).

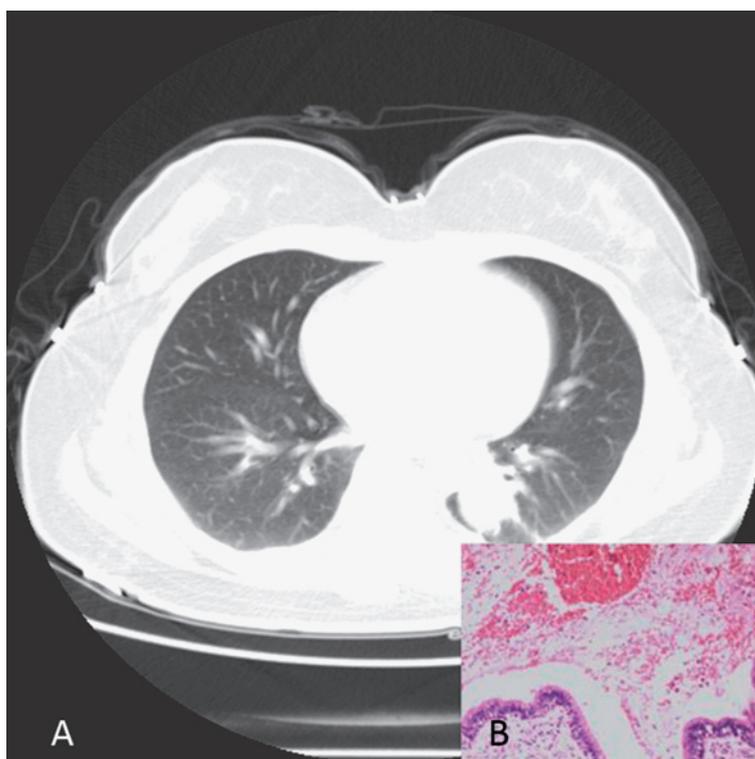


Fig. 1 (A) Chest CT revealed a 27×40 mm heterogeneous low density mass located in the left lower lobe. (B) Histopathology of the resected lung

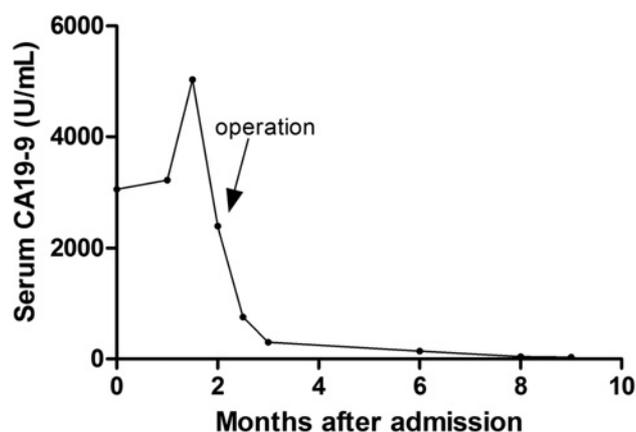


Fig. 2 Serum CA19-9 levels prior to and after operation of pulmonary sequestration. CA19-9, carbohydrate antigen 19-9

### Discussion

Our patient presented with acute hepatitis and an increased CA19-9 level. Significant elevation of serum CA19-9 has been reported in several publications in connection with acute liver failure<sup>10</sup>, chronic viral hepatitis<sup>11</sup> and liver cirrhosis<sup>12</sup>. However, in our patient, after one month of treatment for acute hepatitis, the liver enzymes recovered but the serum CA19-9 level was even higher (5,031.5 u/mL), indicating that the elevated CA19-9 level

was not related to the acute hepatitis. There have been no reports of any association between acute hepatitis and pulmonary sequestration, and our case did not support any link between acute hepatitis and pulmonary sequestration, either.

An association between pulmonary sequestration and elevated serum CA19-9 levels has been reported by several Japanese investigators since it was first identified by Shiota in 1988. In order to better understand our case, we conducted electronic searches of pulmonary sequestration and elevated serum CA19-9 levels in medical databases worldwide. We found 15 clinical cases, which are summarized in **Table 2**. These reported cases included 11 females and 5 males with an average age of 40 years (20–64 years), suggesting higher morbidity in women than in men. Moreover, the majority (80%) of the cases were of intralobar sequestration, which reflects the higher occurrence of intralobar sequestration than extralobar sequestration. The average serum CA19-9 levels in these reported cases was 1,060.7 U/mL (range: 73.8 U/mL to 3,051.1 U/mL), making our case the highest reported serum CA19-9 levels. Steinberg et al. claim that higher levels of serum CA19-9 (>1,000 U/mL) indicate gastrointestinal tract cancer, especially with a specificity of more than 99% for pancreatobiliary cancer<sup>13</sup>. However, no malignan-

Table 2 Pulmonary sequestration complicated with elevated CA19-9 levels in the literature

Author (year)	Sex	Age	Type	CA19-9 levels	Case feature	Healing time
Shiota et al (1988)	Female	38	intralobar	1,000 U/mL	First reported case	5 months
Uyama et al (1989)	Female	23	intralobar	992 U/mL	With calcification and elevated CEA	NA
Kugai et al (1996)	Male	34	extralobar	395 U/mL	With aspergillosis	42 days
Nakamura et al (1997)	Female	39	intralobar	2,418 U/mL	With elevated CA125 and NCC-ST-439	142 days
Ishii et al (1997)	Female	20	intralobar	539.1 U/mL	With elevated CEA, and SLX	1 months
Sekiya et al (1999)	Female	44	intralobar	1,911 U/mL	With aspergillosis and elevated CA125 and CEA	2 months
Yagyū et al (2002)	Male	29	intralobar	496.2 U/mL	With elevated CA125	4 months
Armbruster et al (2004)	Female	64	extralobar	>250 U/mL	Intra-abdominal sequestration	2 months
Matsuoka et al (2006)	Female	62	intralobar	73.8 U/mL	Misdiagnosed as lung cancer	1 month
Fontana et al (2007)	Female	40	extralobar	2,900 U/mL	NA	2 months
Ambiru et al (2009)	Male	62	intralobar	>500 U/mL	NA	NA
Morikawa et al (2011)	Female	32	intralobar	105.3 U/mL	With aspergillosis	1 month
Ahn et al (2012)	Male	29	intralobar	300 U/mL	With bronchiectasia	NA
Komatsu et al (2014)	Female	41	intralobar	728 U/mL	With ovarian cysts and elevated CA125	2 months
Han et al (2014)	Male	48	intralobar	790.6 U/mL	With left upper abdominal bloating	2 months
Present study	Female	39	intralobar	3,051.1 u/mL	With highest levels of CA19-9	6 months

NA=not available, CA19-9=carbohydrate antigen 19-9, CEA=carcino embryonic antigen, CA125=cancer antigen 125

cies were detected in these reported cases after various examinations, although one patient was misdiagnosed with lung cancer<sup>14</sup>. In the majority of the reported cases, immunohistochemical staining of CA19-9 in resected tissue was also performed, demonstrating local CA19-9 in the bronchial and alveolar epithelia of sequestered lung<sup>9,15-19</sup>.

The exact mechanism of elevated CA19-9 in pulmonary sequestration is not clear. According to the literature, there are two possible explanations: one is that CA19-9 might be synthesized and secreted by normal bronchial epithelial cells in the sequestered lung, which then gradually enter the blood stream<sup>20</sup>; the other is that lung epithelial cells chronically infected with *Aspergillus* or other pathogens cause the proliferation of bronchial epithelial cells and synthesis of CA19-9<sup>21</sup>. Our patient was not tested for *Aspergillus* species, so infection could not be confirmed. However, histological examination of resected tissues revealed chronic mucopurulent inflammation of the bronchial mucosa and the formation of micro abscesses, which may indicate a microbial infection. Moreover, confirmation of infection with aspergillosis has been reported in three patients<sup>22-24</sup>, leading us to suspect that the elevated CA19-9 level in our patient was due to aspergillosis infection. Alternatively, CA19-9 could have first synthesized and accumulated in the lesion and then been transferred into the bloodstream through the mucosa of the cyst walls, leading to a high level of CA19-9.

Pulmonary sequestration is uncommon, with an estimated incidence in 0.15% to 1.7% of patients world-

wide<sup>25</sup>. Despite its rarity, these lesions are considered to be of clinical importance. Standard treatment for pulmonary sequestration is resection, which is often accomplished by video-assisted thoracoscopic surgery. Among 16 reported cases, 13 had an average healing time of 2.8 months and 9 reported that the serum CA19-9 levels rapidly decreased to normal range surgery within 1 or 2 months of surgery. However, our patient took 6 months to recover to a normal level, which might have been because of the higher initial levels of CA19-9.

To the best of our knowledge, this is the first report of an elevated serum CA19-9 level in a patient with acute hepatitis and pulmonary sequestration. The reported cases of pulmonary sequestration and elevated CA19-9 levels indicate that CA19-9 is not a specific marker of digestive tract cancers, although it could be a diagnostic marker of pulmonary sequestration. However, not all patients with pulmonary sequestration have elevated serum CA19-9 levels. An understanding of the mechanism of CA19-9 elevation in pulmonary sequestration will clarify the correlation between CA19-9 and pulmonary sequestration. In conclusion, we have reviewed the literature and reported on a patient with pulmonary sequestration and an elevated levels of CA19-9, a diagnostic marker for gastroenterologists and pulmonologists. Elevated serum CA19-9 might be a helpful adjunctive marker to identify pulmonary sequestration when CT-scans do not reveal anomalous systemic vessels.

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**Conflict of Interest:** The authors declare no conflict of interest.

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