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Case Report

Chronic bronchitis with fungal infection presenting with marked elevation of serum carbohydrate antigen 19-9: a case report

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Abstract: Carbohydrate antigen 19-9 (CA19-9) is the most frequently applied serum tumor marker for diagnosis of cancers in the digestive organs. However, some patients with benign diseases can have elevated serum levels of CA19-9 as well. The current study presents a 55-year-old female who was admitted to our hospital for further evaluation of a nodular cavity shadow in the right lower lobe and clarification of the cause of the marked elevation of serum CA19-9 levels. Abdominal MRI and gastrointestinal endoscopy did not find any malignancy. As lung cancer cannot be excluded in this patient, a video-assisted thoracoscopic surgery was carried, intraoperative and postoperative biopsy analysis both suggested chronic bronchitis with fungal infection (due to Histoplasma capsulatum or Penicillium marneffei) and organization. Immunohistochemistry showed marked positive staining for CA19-9 in the damaged lung tissue. The CA19-9 levels quickly returned to the normal range following lobe resection. Therefore, the marked elevation of serum CA19-9 levels, in this case, may have resulted from the chronic bronchitis with fungal infection.

Keywords: Carbohydrate antigen 19-9, chronic bronchitis, fungal infection, immunohistochemistry

Introduction

Carbohydrate antigen 19-9 (CA19-9) levels have been established as a useful tumor marker for gastrointestinal cancers, especially biliary tract and pancreas cancers [1-3]. However, marginal increase of serum CA19-9 levels can also be in benign diseases, such as pancreatitis, liver cirrhosis and diabetes mellitus [4-6]. Furthermore, we and other investigators have reported elevated serum levels of CA19-9 in patients with nonmalignant respiratory diseases, such as tuberculosis (TB), bronchiectasis, pulmonary sequestration, idiopathic interstitial pneumonia (IIP) and collagen disease-associated pulmonary fibrosis (CDPF) without malignant disease in any sites [7-10]. Elevated serum CA19-9 levels may be related to poor prognosis for patients with IIP and CDPF [10]. The current study presents a case of chronic bronchitis with fungal infections, which led to marked elevation of serum CA19-9 levels. This study was approved by the Ethics Committee of Tongji Hospital (Wuhan, China). Witten informed consent was obtained from the patient.

Case report

A 55-year-old female was admitted to the Tongji Hospital (Wuhan, China) presenting with a nodular shadow in the right lower lobe and marked elevation of serum CA19-9 levels. The patient was accidently discovered a high serum CA19-9 level of 494.39 U/ml (normal range, 0~37 U/ml) during a regular medical check-up. She had no obvious symptoms all the time, the serum CA19-9 levels kept rising in the next tests. Whole body PET/CT scan revealed an old tuberculosis lesion at the right lower lobe, she was administered with one year of anti-tuberculous therapy (rifampicin + rimifon + ethambutol), while the shadow in the right lower lobe had no significant change, and the serum CA19-9 level increased to 1197.14 U/ml.

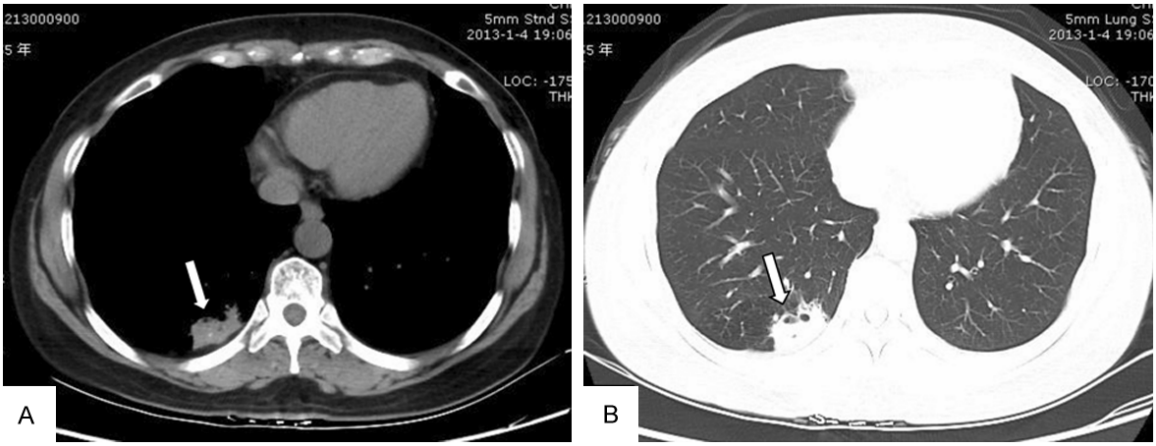

Figure 1. Chest high-resolution CT scanning on admission showed a nodular cavity shadow in the right lower lobe [(A) mediastinal window, (B) lung window].

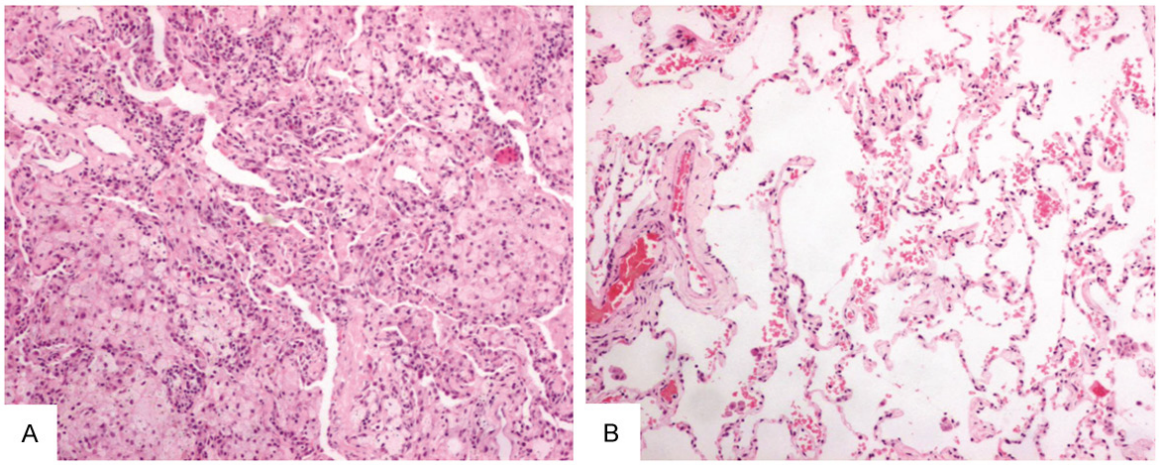

Figure 2. Postoperative pathologic evaluation of the damaged lung (A) and normal lung tissues (B) by hematoxylin and eosin (HE) staining. (Magnification, × 100).

The patient was a soldier and a non-smoker, had a history of hysteromyoma resection ten years ago. The physical examination showed no abnormalities and the laboratory examination revealed the serum CA19-9 level increased to 1,212.04 U/ml, the other tumor markers (CEA, NSE, CYFRA21-1, SCC, AFP, CA125, CA15-3, CA72-4) were all in the normal range. Mycobacterium tuberculosis antibody test indicated the negative result. To exclude the possibility of an underlying abnormal malignant lesion, upper and lower gastrointestinal endoscopy, abdominal ultrasonography, abdominal computed tomography (CT) and magnetic resonance cholangiopan creatography (MRCP) were performed with no specific abnormalities identified. Chest high-resolution CT scanning indicated a nodular cavity shadow measuring 3 cm × 3 cm in the right lower lobe (**Figure 1**). As malignant lesions cannot be excluded in the right lower lobe, an exploratory video-assisted thoracoscopic surgery was carried, a 4.5 × 3 × 3 cm solid mass was found in the posterior basal segments of the right lower lobe, and enlarged lymph nodes in the hilum. The intraoperative frozen sections reported hyperplasia in the bronchial epithelial and no tumor cells were found on frozen sections. The patient then underwent a right lower lobe resection, postoperative pathologic evaluation of the resected lung segment revealed abundant chronic inflammatory cell infiltrated within the bronchial or bronchiolar walls, accumulation of lipid-storing foam histiocytes and neutrophils were

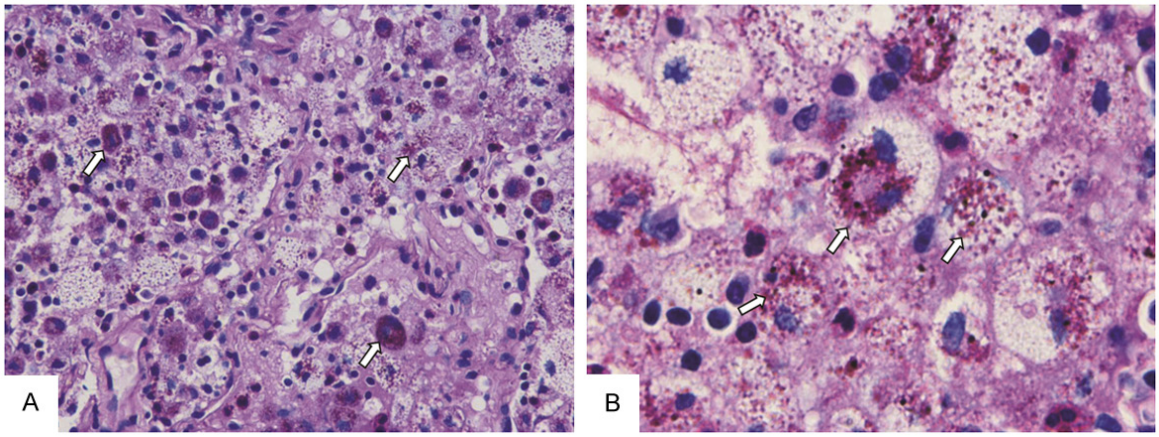

Figure 3. PAS staining of the damaged lung tissues revealed some 1~4 μm positive granular structures in the cytoplasm. [Magnification, (A) × 400, (B) × 1000].

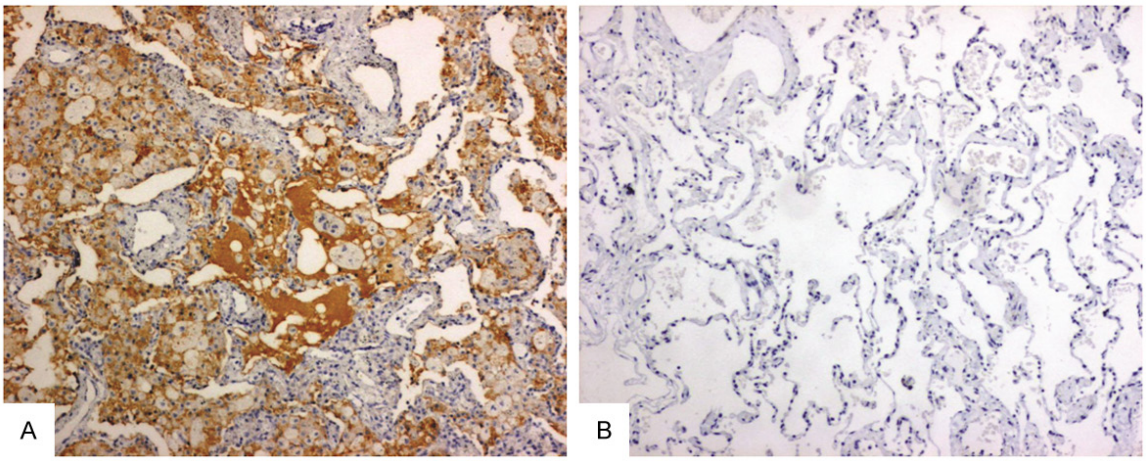

Figure 4. Immunohistochemical staining demonstrated (A) marked staining of carbohydrate antigen 19-9 in the damaged lung tissue, particularly in the mucus of the cysts, but (B) weak or no staining in the normal lung tissue (magnification, × 100). The reaction was amplified using the streptavidin-biotin-peroxidase method and diaminobenzidine was used as a chromogen.

seen in some alveolar regions, and organization of local lung tissues developed (**Figure 2**). PAS staining revealed some 1~4 μm positive granular structures in the cytoplasm of histiocytes under oil immersion lens (**Figure 3**). The final pathological diagnosis was chronic bronchitis with fungal infection (due to Histoplasma capsulatum or Penicillium marneffei) and organization. Unfortunately, we did not find any fungus from the patient's sputum post-operation.

Immunohistochemical staining using a monoclonal antibody against human CA19-9 (Maixin Biotechnology, Fuzhou, China) demonstrated marked positive staining for CA19-9 in the ciliated cylindrical epithelia, alveoli and particularly in the mucus of the cysts (**Figure 4**). Following pulmonary lobectomy, the serum CA19-9 levels rapidly decreased to 317.6 U/ml, then 172.31 U/ml, and finally within the normal range (**Figure 5**).

Discussion

CA19-9 is widely accepted as a valuable marker for pancreaticobiliary cancer [11]. CA19-9 value over 1,000 U/ml usually indicates a digestive cancer and has been reported to have a specificity over 99% for pancreatic cancer [12]. However, elevated concentrations can also occur in other cancers (gastric, colon, hepatic, ovarian, endometrial, pulmonary, or urothelial carcinomas) [13, 14]. In rare conditions, marginal increase of serum levels of

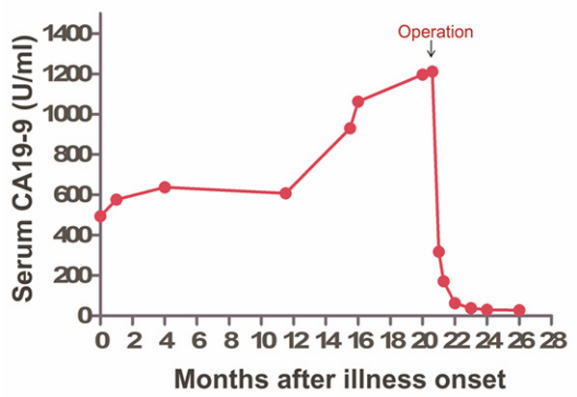

Figure 5. Serum CA19-9 levels after illness onset and following surgery. CA19-9, carbohydrate antigen 19-9.

CA19-9 can also be detected in the following benign conditions: i) CA19-9 production increase due to proinflammatory cytokines stimulation or proliferation of non-cancerous tissues, such as pancreatitis, pancreatic cysts, cholangitis, bronchial cysts, bronchiectasis and ovarian cysts; ii) CA19-9 discharge pathway obstruction, such as pancreatic or cholangial duct stenosis due to gall stones and papillitis; and iii) CA19-9 metabolic disorders, such as chronic hepatitis, diabetes mellitus and chronic glomerulonephritis [15, 16]. Successful identification of increased serum CA19-9 levels from malignancy and benign diseases is important to prevent unnecessary health expenses and needless pain for patients, as proper treatment of benign conditions may result in sudden normalization of serum CA19-9 levels.

In the current study, the patient presented with asymptomatic nodular shadow in the right lower lobe and marked elevation of serum CA19-9 levels was initially suspected of having pulmonary TB, as some Japanese investigators have reported increased CA19-9 levels in the serum and bronchoalveolar lavage (BAL) fluid for TB patients. However, the shadow had no significant change after one year of anti-tuberculous therapy, and the serum CA19-9 level unexpectedly increased to a higher level. No evidence of malignancy was detected in other organs, the patient was advised to an exploratory video-assisted thoracoscopic surgery, intraoperative and postoperative biopsies analysis suggested chronic bronchitis with fungal infection, hyperplasia in the bronchial epithelial and organization. Immunohistochemistry demonstrated strong positive staining for CA19-9 in the damaged lung tissue. Unfortunately, we could not culture any fungal for sputum culture after surgery, this may be because that deep sputum specimen cannot be obtained in this patient for postoperative pain. Anyhow, the serum CA19-9 levels rapidly decreased to normal range following lobec-tomy.

Increased CA19-9 levels in nonmalignant respiratory diseases have been reported in previous studies, mainly by Japanese and Korean investigators [8, 10, 17-19]. Matsuoka et al demonstrated remarkably high levels of CA19-9 ranging from 210 to 95,000 U/ml in bronchial mucus obtained from patients without pulmonary diseases, whereas serum antigen levels were normal in all cases examined [20]. This result suggests that CA19-9 can also be synthesized and secreted by normal epithelial cells of central airways and/or respiratory glands, not just only by pancreatic and biliary ductular cells.

The marked high value of serum CA19-9 obtained in our case is thought to be multifactorial. Firstly, Histoplasma capsulatum, suspected in this case by PAS staining, can induce the host to produce interleukin-1, 12, 17, 23 [21-23], these proinflammatory cytokines, along with those produced by neutrophils, stimulate proliferation of the bronchial epithelial cells, which attributed to increased CA19-9 production. Secondly, CA19-9 released into the mucus of the cysts cannot be discharged by normal expectations because of local tissue organization and pulmonary consolidation, which results in an abundant accumulation of CA19-9 in the alveoli. Additionally, pulmonary tissues with fibrosis and organization are usually local hypoxia [24], recent studies suggest that hypoxia induces the transcription of several glycogenes involved in CA19-9 synthesis, including glucose transporter GLUT1, UDP-galactose transporter UGT1, sialic acid transporter SIALIN, sialyltransferase ST3O and some other genes closely related to carbohydrate metabolism [25-27]. Overall, these reasons may explain the increased CA19-9 levels in the damaged lung tissues. However, the reason why increased CA19-9 levels in the lung result in elevation of serum CA19-9 has not been well understood, one of our previous reports described a patient with pulmonary sequestration presenting with marked elevation of serum CA19-9 could achieve obvious decrease in serum CA19-9 after antibiotic therapy [9], we

inferred that injured mucosa of the cyst walls by inflammation and the architectural disorganization may be the direct pathways for CA19-9 to transfer into blood from alveolus.

In conclusion, the present study suggests that serum level of CA19-9, which has been widely accepted as a tumor marker in gastrointestinal cancers, can also be elevated in patient with nonmalignant lung disease. Therefore, it is important for clinicians, especially digestive physicians to be aware of the nonmalignant respiratory diseases that are associated with elevated serum CA19-9 levels in patients without cancer in any site. In addition, the mechanism of the elevation of serum CA19-9 in different condition is still unresolved and requires further basic investigations.

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Disclosure of conflict of interest

None.

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