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## Pulmonary lesions in the course of gastric cancer — two cases of Bard's syndrome

The authors declare no financial disclosure.

### Abstract

The Bard's syndrome is a medical condition related to miliary dissemination of gastric cancer to the lungs. Difficulties in diagnosis are associated with the need of differentiation between numerous diseases, which may manifest as disseminated lesions in the lung parenchyma on chest radiograph. Despite the advanced proliferative process, primary focus of neoplasm frequently remains subclinical. Metastatic lesions cause many symptoms in the respiratory system, suggesting primary pulmonary pathology. The Bard's syndrome should be always taken into account in differential diagnosis of disseminated lesions, particularly due to prevalence of gastric cancer. The study presents two cases of patients with disseminated pulmonary lesions, corresponding to gastric cancer metastases on radiological imaging.

**Key words:** gastric cancer, lung metastases, Bard's syndrome, interstitial lung disease

**Pneumonol Alergol Pol 2016; 84: 33–37**

### Introduction

Disseminated pulmonary lesions, seen on chest radiograph performed due to non-specific symptoms in the respiratory system such as dyspnoea or chronic cough, pose a complex diagnostic problem. In differential diagnosis, numerous diseases should be taken into account, such as: tuberculosis, secondary lesions in the course of connective tissue diseases, drugs side effects, exposure to dust and inhaled allergens, lesions of unidentified origin (e.g. idiopathic pulmonary fibrosis) and rarely, lesions associated with malignancies. However, as neoplasms are the second cause of mortality worldwide after cardiovascular diseases, the symptoms in the lungs may be the

first manifestation of proliferative process, whose initial focus remains subclinical.

According to the WHO, gastric cancer was one of the most frequent neoplastic causes of death worldwide. Distant metastases of this tumour locates in lungs twice more frequent among males. The presence of pulmonary metastases in the course of disseminated gastric cancer is called the Bard's syndrome. Apart from single or multiple tumours in the parenchyma of the lungs, metastatic lesions may manifest themselves as lymphangitis carcinomatosa and pleuritis carcinomatosa. As reported in the literature, these kinds of metastases of the gastric cancer shares the feature, that the symptoms in the respiratory system dominate over the symptoms in the ali-



**Figure 1.** Chest radiograph. Symmetrically distributed, disseminated, reticular interstitial thickening

mentary tract. A rare phenomenon are metastatic lesions that due to their morphology, on radiological imaging imitate non-neoplastic interstitial lung diseases [1–4].

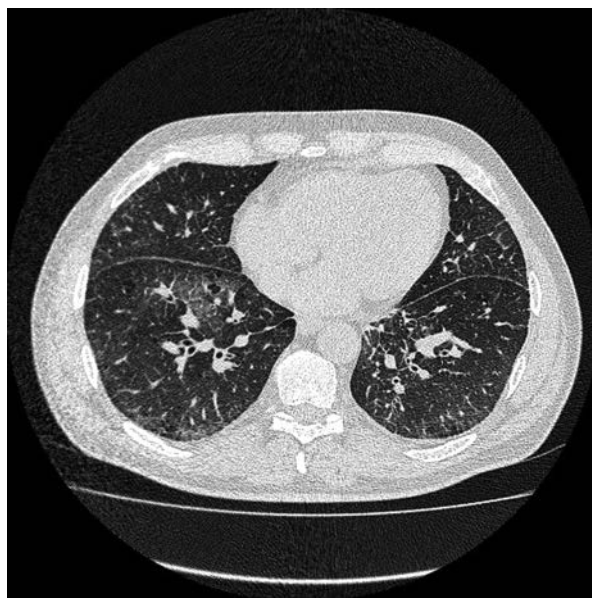
The study reports two cases of patients with advanced, disseminated gastric cancer, who were admitted to the Pulmonology Department because of cough and dyspnea. On the chest radiograph, disseminated pulmonary lesions, suggesting interstitial lung disease were revealed.

### Case 1

51-year old male, admitted to the hospital with the history of cough and increasing exertional dyspnoea for about one month. Laboratory tests did not show any abnormalities. Lung function tests showed obstruction (the Tiffenau index 66%, FEV<sub>1</sub> 77% of predicted value) with negative result of reversibility test, and deteriorated diffusion capacity to the level of 59% of predicted value.

The chest radiograph revealed disseminated ring-shaped interstitial densities of symmetrical distribution (Fig. 1). The imaging diagnosis was complemented by high resolution computed tomography (HRCT) of the chest, which revealed disseminated micropunctual lesions of interlobular septal thickening and interlobar fissures, thickened walls and widened lower lobar bronchi. The small ground glass opacity in the lower lobe of the right lung, similar to local alveolitis was visible (Fig. 2).

Bronchoscopy did not show any pathology, material was sampled for cytologic examination, culture in the direction of *Mycobacterium tuberculosis*, and two specimens from the peripheral area of lung were taken for histopathological exami-



**Figure 2.** Disseminated nodules with thickening of septa and interlobar fissures, thickening of lower lobes bronchial walls and bronchi widening. Slight ground glass opacities in lower, right lobe suggesting local alveolitis

nation. Due to positive tuberculin skin test, before obtaining the results of the culture, anti-mycobacterial therapy (rifamazid, pyrazinamide, ethambutol) and then prednisone were introduced. Cytologic examination of bronchial aspirate did not reveal the presence of neoplastic cells. Histopathological examination of the specimens of the lungs revealed emboli of adenocarcinoma cells. The patient reported the history of chronic gastric ulcer disease. Endoscopic examination of the upper part of the alimentary tract showed embanked ulceration in the gastric mucosa. The examination of the specimens led to the diagnosis of adenocarcinoma. The patient was transferred to the oncology centre of the alimentary tract for further treatment.

### Case 2

A 35-year-old male patient was admitted to the Pulmonology Department due to dyspnoea and cough with low-grade fever persisting for more than ten days. The patient reported the history of exposure to chemical substances such as gases and dust due to his profession of a welder. Laboratory tests revealed leucocytosis 19000/mm<sup>3</sup>, CRP 20 mg/l, anaemia, the presence of antibodies to *Helicobacter pylori* and a positive fecal occult blood test. In bronchoscopy, inflammatory changes of the mucosa of the airways with residual mucous and purulent secretion in the lumen were visualized.



**Figure 3.** Multiple, regularly distributed ground glass opacities, septal thickening, segmental bronchial walls thickening, pleural thickening. Fluid in both pleural cavities

The chest radiograph revealed bilateral, disseminated lesions. In order to extend diagnostic imaging, HRCT was ordered. It displayed multiple, regularly distributed areas of “ground glass” opacity, interlobular septal thickening, thickened pleura and regional thickening of bronchi walls. In addition to that, bilateral pleural effusion was revealed (Fig. 3) Antibiotics, anti-mycobacterial drugs and glucocorticosteroids were included in the therapy. In spite of a 14 day-long therapy, the state of the patient was worsening, dyspnoea at rest and progressive respiratory failure appeared.

The patient was transferred to the hospital of lung diseases, where, due to increasing respiratory failure with accompanying supraventricular tachycardia up to 200/min with episodes of polymorphic ventricular tachycardia and decompensation features of the cardiovascular system, on the third day of hospitalisation, the patient was transferred to the Intensive Care Unit (ICU). At the ICU, the patient was intubated and mechanically ventilated with  $\text{FiO}_2$  0.8–1.0. The echocardiography revealed hypokinesis of the wall of the right ventricle, mitral incompetence of medium degree and indirect features of pulmonary hypertension. Due to extreme right ventricular overload, the patient was qualified for arteriovenous ECMO grafting. Inotropic drugs and nitrogen oxide were introduced. The patient was sedated.

Diagnosis of cardiopulmonary failure cause was supplemented with gastroscopy, which demonstrated rigid infiltration of the body of the

stomach, from which specimens were taken. The histopathological examination displayed adenocarcinoma mucinosum. The corresponding cells were also found during cytological examination of the pleural effusion. Due to diagnosis of disseminated neoplastic process, the ECMO system was removed. The patient died. Post mortem examination revealed cancer of the lesser curvature of the stomach with multiple metastases to mesenteric lymph nodes, neoplastic infiltration to the pancreas and porta hepatis, multiple metastases to the lymph nodes of the posterior mediastinum, lungs, and carcinomatosis of the left pleura.

## Discussion

The interstitial lung diseases include the group of over 150 medical conditions of various etiology. Disseminated lesions, seen in radiological imaging, at the cellular level reflect various in degree, intensive inflammation, and fibrosis of interstitial tissue of the lungs. Similar image may be given by massive, miliary neoplastic pulmonary metastases. They were reported in the course of diverse histological types of neoplasms such as: choriocarcinoma, malignant neoplasms of the respiratory and alimentary systems, as well as the manifestation of the relapse of thyroid carcinoma. It is not known yet, which features of the primary tumour, and which topical circumstances within the vascular rete are responsible for the deposition of the cells in its particular regions, starting metastatic lesions of specific morphology, leading or not to angitis. It seems, that in adenocarcinoma of the stomach, one of predisposing features is the presence of defects in proteins that are responsible for intercellular adhesion and which are typical of diffuse subtype of this neoplasm. Microscopic image of miliary metastases of adenocarcinoma of the stomach is characterised by the presence of single neoplastic cells or their clusters in the lumen of blood and lymphatic vessels of the lungs, sometimes accompanied by thrombi consisting of thrombin and platelets. The lesions constrict or close the lumen of the vessels, both directly or by the pressure from the outside, thus leading to perfusion disorders of the large area of the lungs [5–10].

The above mentioned disorders of the perfusion to ventilation ratio are the cause of clinical manifestation of metastases such as dyspnoea, cough or chest pain. Disseminated lesions create the occlusion of the vessels. It results in increased resistance of pulmonary bed as well, and consequently, in the development of pulmonary hyper-

tension. There are also reports about the cases of acute cor pulmonale being the result of miliary metastases to the lungs. Primary lesion of gastric cancer frequently remains subclinical, however, in case of recurrence, pulmonary symptoms may be added to slowly increasing symptoms in the alimentary tract. In the literature, the case of a patient, in whom ailments in the hypogastrium recurred three years after surgery of gastric cancer, was reported. At the beginning there were no changes on chest radiograph, however the X-ray image during follow-up examination after the therapy with cyclophosphamide showed disseminated lesions that were differentiated between tuberculosis, sarcoidosis, pneumoconiosis and cardiovascular failure. This case differs from the cases reported in our report in the history of gastric cancer, which from the very beginning indicated the possibility of dissemination of neoplastic process as the main reason for the patient's afflictions. In addition to that, symptoms in the respiratory system joined earlier occurring symptoms in the alimentary tract [11].

Due to atypical clinical and radiological image of miliary lung metastases, a correct diagnosis is delayed. Uncharacteristic image of chest X-rays makes the clinicians apply therapies for the diseases which masks this neoplasm. The available literature presents the cases that in differential diagnosis, similarly to the patients reported in the present study, mentioned pulmonary tuberculosis and the attempt to use anti-mycobacterial therapy. Furthermore, a 3-week-long therapy of the female patient with the alleged bronchitis was reported. The patient was treated with prednisone due to based on radiological examination suspicion that she had a pulmonary manifestation of systemic connective tissue disease. There is also a case of a patient with diagnosed pneumonia, who was referred to hospital for further diagnosis only at the moment of acute pulmonary failure in the course of neoplasm dissemination to the lungs. Rapid development of respiratory failure allows to establish a correct diagnosis only during post-mortem examination. The second case that we reported presents the patient in whom the Bard's syndrome was established intravitaly [12, 13].

The radiological image of both patients reported in the present paper did not suggest clearly the involvement of blood and lymphatic vessels of the lungs, although the examination of the lung specimen in the first patient and autopsy of the second one, did reveal lesions of this type. The presence of pulmonary embolism with metastatic neoplastic cells in the course of advanced neo-

plastic disease is a frequent phenomenon, particularly at autopsy. The changes of this type are seldom diagnosed intravitaly, due to coexisting progressive cardiovascular failure. Histological images of these lesions may be divided into two types: pulmonary embolism that has a typical radiological image on angio-CT, and embolic microangiopathy. Microangiopathy on CT may give nonspecific image. There are reports of manifestations in the form of a tree-in-bud pattern, which is associated with the small airways diseases such as infectious bronchiolitis. The carcinomatous lymphangitis is a manifestation of metastases resulting from the involvement of lymph vessels, of which one in four cases does not show changes on chest radiograph. The CT image that shows similar manner of spreading of neoplasm is referred to as 'dot in a box' [10, 14–17].

The radiological image of the chest in patients with disseminated pulmonary metastases of gastric cancer is heterogeneous, and frequently suggests interstitial lung diseases. The lesions described in chest radiographs may take the form of opacities of various diameters. It may have the appearance of nodular, mottling, reticular or streak lesions. The lesions may have predilections for certain pulmonary lobes. In the available literature they were more frequently expressed in the middle and upper lobes. Whereas in patients reported in our study, lesions were distributed evenly and symmetrically. In addition, pleural effusion may appear. Miliary nature of shadowing in the parenchyma of the lungs may suggest a specific process (TB). On CT, Bard's syndrome may be revealed by thickened interlobular septum and thickened tissue surrounding bronchovascular bundles. Other symptoms are linear, longitudinal and ground glass opacities, which reflect disorganisation of the correct structure of the lungs. In spite of the abundance of images, none of them is pathognomonic of neoplastic diseases. In the literature, we can find reports about X-rays with disseminated metastases of gastric cancer to the lungs, but corresponding tomograms are rare and concern other histological types of neoplasm [13, 18].

In many patients, despite the use of imaging diagnosis and minimally invasive methods such as bronchofiberscopy with transbronchial biopsy, final diagnosis is not established. As transbronchial biopsy of the lung allows to reach diagnosis only in medical conditions with the involvement of peribronchial tissue, a diagnostic process is supplemented with biopsy performed under videothoracoscopic control. The literature data indicate high efficiency of this type of lung

biopsy in obtaining material for the establishment of final diagnosis (95% up to 100% in some reported cases). It is comparable to data concerning open lung biopsy. Among complications associated with lung biopsy under thoracoscopic control, the most frequent is pneumothorax, the necessity of mechanical ventilation due to respiratory decompensation, and haematoma in the place of insertion of a videothoracoscope. Mortality within 60 days from the procedure amounts to about 5% and is related to risk factors such as lowered diffusing capacity for carbon monoxide and pulmonary arterial hypertension. Despite potential risk, videothoracoscopic biopsy is a vital element in a diagnostic process in disseminated lesions, mainly in the event of difficulty in making clear diagnosis using less invasive techniques [19–21]. In the case of our first patient, sample taken during bronchofiberoscopy allowed to diagnose dissemination of neoplastic process, whereas clinical condition and rapid progress of the disease in the second patient did not permit to use videothoracoscopy.

The Bard's syndrome is a crucial medical condition, which should be taken into account during differential diagnosis of disseminated pulmonary lesions in the chest radiograph or CT. During diagnostic process that tries to identify interstitial lung diseases, it is always necessary to exclude neoplastic diseases. In unclear cases, biopsy of peripheral lung tissue or endoscopy of the upper segment of the alimentary tract may accelerate the establishment of an appropriate diagnosis and administration of treatment.

### Conflict of interest

The authors do not declare conflict of interest.

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