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ТРУДНОСТИ ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ БРОНХООБСТРУКТИВНОГО СИНДРОМА

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The Difficulties of Differential Diagnosis of the Bronchial Obstruction Syndrome

Резюме

Бронхообструктивный синдром представляет собой нарушение бронхиальной проходимости функционального или органического происхождения, который проявляется одышкой, приступами удушья, кашлем, тахикардией. Наиболее распространёнными причинами бронхообструктивного синдрома являются хроническая обструктивная болезнь легких и бронхиальная астма. В некоторых случаях причиной бронхиальной обструкции являются опухоли или метастазы опухолей в легкие. В статье описан клинический случай бронхообструктивного синдрома, показывающий, что все больные с бронхиальной астмой, при отсутствии эффекта от назначенной адекватной базисной терапии, с отсутствием контроля над заболеванием, должны быть хорошо обследованы на предмет альтернативного диагноза. В нашем случае тщательное обследование больной позволило врачу аллергологу диагностировать центральный рак легкого с метастазами в лимфоузлы средостения. Особенностью случая является первичная резистентность к ингибиторам тирозинкиназы, выявленная при генетическом исследовании, что определило схему дальнейшей полихимиотерапии. Данный клинический случай доказывает необходимость проведения дифференциальной диагностики, с комплексным подходом и использованием различных методик обследования.

Ключевые слова: *бронхиальная астма, бронхообструктивный синдром, ингибиторы тирозинкиназ, немелкоклеточный рак легких, рецептор эпидермального фактора роста*

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Abstract

Bronchial obstructive syndrome is a violation of bronchial patency of functional or organic origin, which is manifested by shortness of breath, suffocation attacks, cough, tachycardia. The most common cause of bronchial obstructive syndrome is chronic obstructive pulmonary disease and bronchial asthma. In some cases, the cause of bronchial obstruction is tumors or tumor metastases to the lungs. The article describes a clinical case of bronchial obstructive syndrome, showing that all patients with bronchial asthma, in the absence of an effect from the prescribed adequate basic therapy, with no control over the disease, should be well examined for an alternative diagnosis. In our case, a thorough examination of the patient allowed the allergist to diagnose central lung cancer with metastases to the lymph nodes of the mediastinum. A feature of the case is the primary resistance to tyrosine kinase inhibitors, revealed during a genetic study, which determined the scheme of further polychemotherapy. This clinical case proves the need for differential diagnosis, with a comprehensive approach and the use of various examination methods.

Key words: *bronchial asthma, bronchial obstruction syndrome, tyrosine kinase inhibitors, non-small cell lung cancer, epidermal growth factor receptor*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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TKI — tyrosine kinase inhibitors, VC — vital capacity, FEV_1 — forced expiratory volume in one second

Introduction

Bronchial obstructive syndrome is a complex of symptoms associated with impaired bronchial patency of functional or organic origin. The most common complaints in bronchial obstruction are: dyspnea, asthma attacks, productive or unproductive cough, and tachycardia [1].

According to literature data, bronchial obstructive syndrome is a challenging diagnosis that combines a heterogeneous group of diseases and a variety of risk factors, prognosis and treatment methods [2].

Chronic obstructive pulmonary disease and bronchial asthma are the most common causes of bronchial obstructive syndrome [3]. One of the common causes of bronchial obstruction is tumors or their metastases in the lungs. Most lung cancers are known as primary tumors, which include carcinomas that originate from epithelial cells. The clinical picture of lung cancer during physical examination in most cases manifests itself in the late stages. The earliest signs of a lung tumor are: persistent cough (can be either unproductive or productive), dyspnea (inspiratory or mixed) without chest pain, hemoptysis, general weakness, and fatigue [4].

In clinical practice, computed tomography is used to diagnose lung cancer. Morphological verification of the diagnosis is performed using fibrobronchoscopy with biopsy, which allows diagnosing central lung cancer in the absence of X-ray signs [4].

Both standard chemotherapy regimens and targeted drugs — 1st and 2nd generation EGFR tyrosine kinase inhibitors (TKI) (Gefitinib, Erlotinib, Afatinib) — are used to treat patients with non-small-cell lung carcinoma. In 60% of cases, resistance occurs after 8–12 months of using these drugs. For this reason, tyrosine kinase inhibitors are prescribed as second-line therapy. If a mutation in the EGFR gene is detected during molecular genetic research prior to the prescription of TKI, resistance is regarded as primary. The T790M mutation (replacement of the amino acid residue of threonine with methionine at position 790) makes TKI use ineffective [5].

Case report

We present a clinical case from the Department of Allergology of the Regional Clinical Hospital in Krasnoyarsk. Patient H., 58 years old, was referred to an allergist at the Regional Clinical Hospital to clarify the diagnosis in November 2018 with complaints of paroxysmal cough in the morning with difficulty to discharge mucus sputum and following hoarseness, occasional feeling of heaviness, chest congestion, wheezing, inspiratory dyspnea when climbing stairs up to the 2nd floor.

The first symptoms appeared after emotional stress in November 2017. Patient took acetylcysteine on her own. She did not have nocturnal symptoms of suffocation; she did not use bronchodilators. She was examined by a local allergist in January 2018. According to the medical history, the patient's maternal grandfather suffered from bronchial asthma. Patient does not smoke. During the last four years, a paroxysmal unproductive cough was noted upon contact with household chemicals. During the last 1.5 years, a dry paroxysmal cough was noted after a viral infection. History of allergy to beta-lactam antibiotics (anaphylactic shock and urticaria). The patient lives in a panel building, sleeps on a polyester pillow, has a dog.

Spirometry and bronchodilator test results, dated January 31, 2018: vital capacity (VC) was 101%; forced expiratory volume in 1 second (FEV1) — 89%; FEV1/VC) — 86; test with salbutamol 400 mg — negative, increase in FEV1 — by 2%. Conclusion: external respiration function within normal. Scarification tests were performed with household, epidermal and pollen allergens. Sensitization was not detected. Based on the clinical picture, medical history, physical examination and further investigations, non-allergic bronchial asthma was diagnosed first. Controller medications were prescribed: beclomethasone / formoterol 100/6 μg, 1 inhalation twice a day; salbutamol 100 μg, 1–2 inhalations on demand in case of suffocation. Despite the therapy, episodes of labored breathing persisted, as well as dyspnea at moderate physical exertion; episodes of dry cough became more frequent; wheezing labored breathing appeared at night, and hoarseness of the voice was noted; a decrease in body weight (four kg loss in two months) was observed with preserved appetite.

In October 2018, the patient was repeatedly attended to by an allergist at a local outpatient clinic. According to the data of thyroid ultrasound and chest X-ray, no abnormality was revealed. The patient was prescribed the following treatment: ipratropium bromide/fenoterol 1 ml four times a day via a nebulizer, methylprednisolone 4 mg — three tablets per day for seven days, montelukast 10 mg at night. During therapy, the frequency of asthma attacks decreased, but coughing, wheezing, and hoarseness persisted. Due to the lack of monitoring the symptoms of bronchial asthma, she was referred for consultation with an allergist at the Regional Clinical Hospital in Krasnoyarsk and was hospitalized on November 21, 2018, in the Allergology Department for symptom management and controller medication adjustment.

Physical examination findings: at auscultation — harsh breathing is conducted over all pulmonary fields, rales are not heard, respiratory rate is 21 per minute, SaO_2 97%. Laboratory findings were within normal limits. Spirometry and bronchodilator test revealed mixed dysfunction of external respiration: VC — 53–75%; FEV1 — 47–50%; FEV1/VC — 73-77; bronchodilation test (salbutamol 400 μg) negative, increment — 3%. Chest X-ray in two projections: the pulmonary fields are characterized with increased pneumatization, without shadowing, the pulmonary pattern is diffusely strengthened, the roots are structural, the mediastinal shadow is not displaced, the aorta is compressed, elongated, the interlobar pleura is densified on the right. The diaphragm contour is clear, even, the sinuses are free (Fig. 1).

Despite the presence of allergic history, respiratory symptoms, dysfunction of external respiration with a moderate decrease in VC, a negative bronchodilation test, and the absence of the effect of the prescribed therapy required further investigations. Tracheobronchoscopy revealed bilateral diffuse moderate bronchitis with mild hypersecretion. Deformation of the right middle lobe and lower lobe bronchi. A biopsy of the middle lobe and lower lobe bronchi was conducted (Fig. 2).

On November 30, 2018, multislice computed tomography (MSCT) of the chest was performed, mass lesion in the root of the right lung, measuring 30.2 × 33.8 × 42.5 mm, with cord-like tuberous contours was defined. The lobe bronchi are compressed due to the lesion, the stump of the middle lobe bronchus is determined. In the right middle lobe, signs of lymphangitic carcinomatosis are determined. Mediastinum structures are preserved, not displaced. No enlarged lymph nodes. There is no

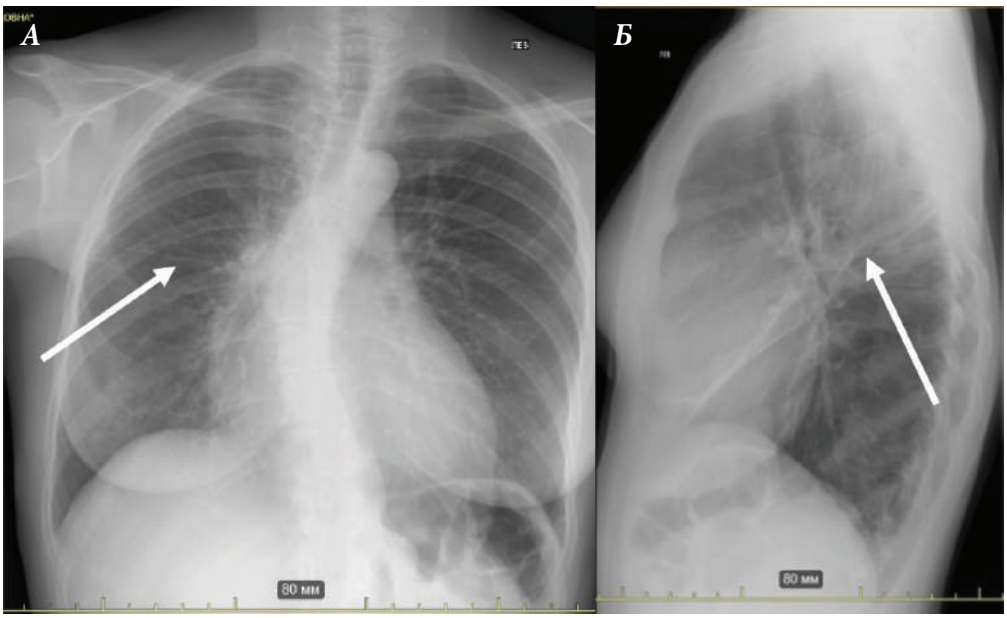

Figure 1. *Radiography of chest organs in 2 projections dated 23.11.2019.*
a) direct projection,
b) lateral projection

pleural effusion. Pericardial effusion, pericardium thickness is 27.4 mm (Fig. 3).

When examined by an otorhinolaryngologist, no abnormality was detected. Three-fold cytological examination of sputum did not reveal Mycobacterium tuberculosis. Histopathological examination of the bronchus showed gland-like structures representative of bronchial adenocarcinoma. The patient was diagnosed with central cancer of the right lung. The patient was referred to an oncologist at the A. I. Kryzhanovsky Krasnoyarsk Regional Clinical Oncology Center (KRCOC).

In April 2019, the patient was diagnosed with stage IIIa (T3NxM0) central cancer of the right lung. Deformation of the right middle lobe and lower lobe bronchi. Mediastinal lymph node metastases. The EGFR+ mutation was detected at the KRCOC during the cytogenetic examination of the lung biopsy specimen, the T790M mutation, ALK — negative. Therefore, the patient has primary resistance to tyrosine kinase inhibitors. According to the histological conclusion, a polychemotherapy course was prescribed in the EC regimen (Etoposide and Cisplatin).

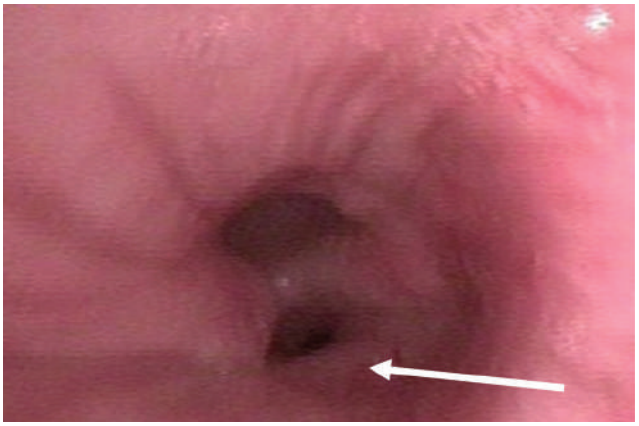

Figure 2. *Tracheobronchoscopy dated 26.11.2018*

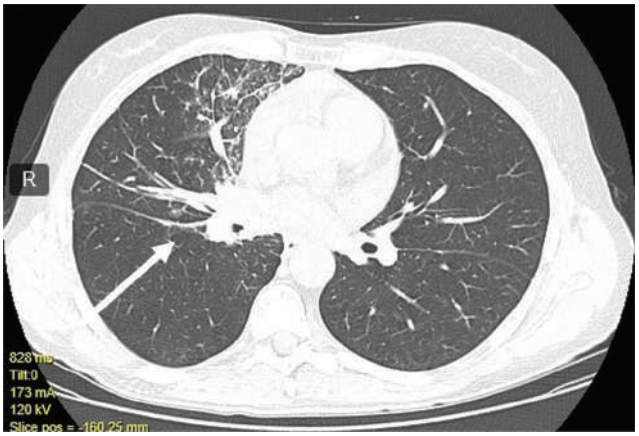

Figure 3. *MSCT of thoracic organs dated 30.11.2018*

Discussion

The incidence of lung cancer has increased dramatically in many countries around the world in recent years. More than 1.2 million new cases of lung cancer are reported annually in the world. In Russia, lung cancer also ranks 1st among oncological diseases, accounting for 12% of cases. Central lung cancer accounts for 60–80% of all cancer cases [6, 7]. Incidence statistics are sex-related. In men, lung cancer is the most common cancer and accounts for 16.7% of all cases. In women, it is significantly lower and amounts to 8.8% [7].

Among the risk factors for central lung cancer, smoking ranks first — 79.1%, and followed by occupational hazards (metal processing — 8.3%; chemical production — 5.6%, etc.) [8]. Therefore, primary care physicians should be less stereotypical about the central lung cancer diagnosis and suggest this disease in such cases.

The early clinical symptom in patients with central lung cancer is cough: according to the literature, it occurs in up to 70% cases. The second most common symptoms are chest pain (38%) and dyspnea (37.9%) [8]. In this case, cough upon contact with chemicals in the patient appeared four years before the diagnosis was established. However, since the above-described stereotype and characteristic medical history data (grandfather with BA, allergic history), BA appeared to be a more suitable diagnosis.

Current difficulties in central lung cancer diagnosis are also associated with the predominance of its peribronchial form, which, for a long time, does not cause significant narrowing of the bronchus lumen or its obstruction [6]. In this case, clinical signs of bronchial obstructive syndrome appeared 1.5 years before the diagnosis. The presence of bronchial obstructive syndrome and the absence of the effect of the BA controller medications made it possible to doubt the earlier diagnosis. Further investigations (tracheobronchoscopy and chest MSCT) revealed signs of central lung cancer. The patient was referred to an oncologist for further treatment.

Conclusion

The presented clinical case suggests that all patients with bronchial asthma, if the prescribed treatment has no effect and without monitoring the disease, should be carefully examined for an alternative diagnosis. The described clinical case proves the need for differential diagnosis with an integrated approach and the use of various examination methods. The clinician should remember that bronchial tumors are a common cause of persistent bronchial obstructive syndrome. The focus should be on the fact that cancer must be excluded if the prescribed controller medications are ineffective.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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