e-ISSN 1941-5923 © Am J Case Rep. 2024: 25: e943798 DOI: 10.12659/AJCR.943798

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Received: 2024.01.13 Accepted: 2024.03.27 Available online: 2024.04.26 Published: 2024.06.15	Lung Lesions: Differential Diagnoses Beyond Cancer			
Authors' Contribution:ABCDEF1Study Design AABDE2Data Collection BDE2Statistical Analysis CDE2Data Interpretation DManuscript Preparation ELiterature Search FFunds Collection GFF	Paweł Jurczak 💿 Anna Romaszko-Wojtowicz 💿 Anna Doboszyńska 🗈	 School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland Department of Pulmonology, School of Public Health, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland 		
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Case series				

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> Female, 75-year-old • Female, 68-year-old • Male, 68-year-old • Male, 66-year-old Diffuse large B-cell lymphoma • ectopic thyroid tissue • post-traumatic pleural hematoma • tuberculosis of the lungs Dry cough • dyspnea • weight loss

General and Internal Medicine • Pulmonology

Objective: Unusual clinical course

Background: Lung cancer is the most common malignant neoplasm diagnosed worldwide. Early diagnosis and treatment are of great importance for patient's prognosis. A wide variety of pulmonary conditions display clinical and radiological presentation similar to that of lung cancer, and the awareness of their existence can help in making correct diagnoses.

Case Reports: This article presents a description of 4 patients with an insidious type of lesions mimicking pulmonary carcinomas. The first patient was referred to Department with a tumor-like lesion in the right lung. After CT of the chest and core-needle biopsy, the lesion turned out to be an ectopic thyroid tissue. The second patient reported a dry cough and weight loss. A lung nodule mass was revealed in chest CT and the patient was diagnosed with pulmonary tuberculoma. The remaining 2 patients, despite the suspicion of lung cancer, were subsequently diagnosed with a post-traumatic pleural hematoma and diffuse large B cell lymphoma.

Conclusions: Low-dose computed tomography of the chest plays a significant role in the diagnosis of newly detected lesions in the lungs. However, due to the similarity of the image of cancer to that of other diseases, the ultimate diagnosis should be based on the interpretation of full imaging diagnostic tests, clinical presentation, and histopathological examination of the material obtained from the lesion. Analysis of cases enables us to expand our understanding of the diseases that need to be considered in differential diagnosis of a patient with a detected tumor-like lesion in the lungs.

Lung Neoplasms • Lymphoma, B-Cell • Mycobacterium tuberculosis • Thyroid Diseases Keywords:

Full-text PDF:

Patients:

Symptoms:

Final Diagnosis:

Clinical Procedure: Specialty:

https://www.amjcaserep.com/abstract/index/idArt/943798





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Introduction

Lung cancer is the most common malignant neoplasm in the world. Despite the broadly understood medical progress, both the morbidity and mortality of lung cancer tend to increase [1]. Early diagnosis and treatment, as in many other cancers, are significant for the patient's prognosis. The seriousness of the prognosis of lung cancer adds to the importance of an accurate differential diagnosis of pulmonary lesions, which is sometimes difficult. Atypical clinical manifestations of lung cancer can resemble various other, benign conditions, such as pneumonia, lung abscess, scars caused by infections, atelectasis, mediastinal tumors, emphysema, and granulomatous diseases [2]. Benign neoplasms in lungs are relatively rare, constituting less than 5% of all pulmonary tumors, and are often diagnosed incidentally [3]. Such neoplasms can develop in the bronchial tree or in the pulmonary parenchyma, and can grow from epithelial, mesenchymal, or salivary gland cells, or from unidentified cells [4]. Despite the important contribution of CT into the diagnostic process of space-occupying lesions in the chest, the radiographic images obtained do not ensure complete certainty as to the final diagnosis [5]. On the one hand, the use of low-dose computed tomography as a screening test for patients aged 40 years and over, with the history of considerable exposure to tobacco smoke and at least 20 pack-years, contributes to a decrease in mortality owing to the improved detection rate of low-stage lesions. On the other hand, it leads to an increase in the detection of false-positive changes [6,7]. Because of the need to improve techniques for lung cancer detection at an early stage, attempts have been made to use radiological artificial intelligence, liquid biopsy, biomarkers, or microRNA and others [8-12]. Screening tests using chest radiography and sputum culture have not been proven to cause any decline in lung cancer mortality rates [13]. The final diagnosis should therefore be based on a simultaneous analysis of complete imaging diagnostic tests and histopathological examination of the material obtained from the lesion. It is also recommended to include the knowledge of classic diagnostic pitfalls and some rare diseases that can reliably mimic the presentation of lung cancer.

The purpose of this article is to report 4 cases of patients with an insidious picture of lesions imitating lung cancer.

Case Reports

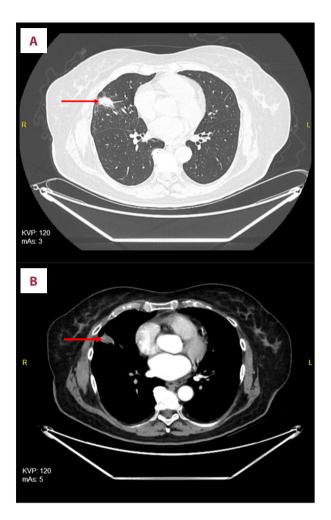
Case 1

A 75-year-old woman who was a former smoker (quit smoking 30 years ago, approximately 30 pack-years), with hypertension and asthma given in the medical history, was admitted to the clinic for diagnostic tests of a tumor-like lesion in the right lung. On admission, she reported worsening health over the past 3 months and periodic dry cough. The laboratory tests did not reveal any abnormal findings. A computed tomography (CT) scan of the chest (Figure 1) showed a nodular lesion 9 cm in diameter, containing calcifications, infiltrating the pulmonary hilum and laterally adhering to the pleura. The lesion connected to a nodular lesion with calcifications situated in the precardiac adipose tissue, and to the thyroid tissue. Additionally, the examination demonstrated visible atelectatic changes in the right lung and ground-glass thickenings as well as a para-pleural nodule, 9 mm in size, in the left lung. The diagnostic procedure included core-needle biopsy of the lesion in the right lung. The histopathological examination revealed



Figure 1. X-ray (A) and CT (B) of the chest of a patient with ectopic thyroid tissue. Red arrow indicates a nodular lesion of the diameter of 9 cm.

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thyroid tissue and a neoplasm was excluded. Eventually, a diagnosis of ectopic thyroid tissue was made.

Case 2

A 68-year-old woman who was a former smoker was admitted to the Pulmonology Clinic with the diagnosis of a nodular lesion in the right lung detected on a thoracic X-ray. The X-ray (Figure 2C) of the chest showed a tumorous mass, 31 mm in diameter, situated in the lower pole of the right lung hilum, as well as parenchymal densities size 77×65 mm in the lower field of the right lung. The patient reported having an intermittent dry cough and had lost 8 kg of weight in the past 2 months. She quit smoking approximately 20 years ago (10 pack-years). The laboratory tests did not show any significant abnormalities. The chest CT scan demonstrated a 24×13 mm peripheral nodule in the right lung and a 12 mm enlarged lymph node in the right hilum (Figure 2A, 2B). Bronchofiberoscopy was performed and bronchial lavage was obtained for culture and cytological examination towards tuberculosis. Next, CT-guided core-needle biopsy of the right lung was done. The biopsy sample showed numerous epithelial cell granulomas with central

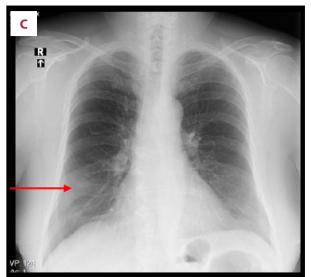


Figure 2. CT scans (A: pulmonary window, B: mediastinal window) of the chest and thoracic X-ray (C) of a patient with tuberculosis granuloma. In A) and B), red arrows point out a peripheral nodule with the dimensions of 24×13 mm in the right lung. In C), red arrow indicates parenchymal densities size 77×65 mm in the lower field of the right lung.

necrosis. No cancerous cells were observed. Considering the entire clinical presentation of the patient, she was diagnosed with tuberculosis and consequently referred for further treatment.

Case 3

A 68-year-old man with a history of hypertension and deep vein thrombosis of both lower legs was admitted to the clinic due to an exacerbation of chronic obstructive pulmonary disease (COPD). He quit smoking 1 year ago, with 40 pack-years in his medical history. He reported having dyspnea at rest and exertion and productive cough for the past 2 days. On physical examination, weakening of vesicular murmur over the pulmonary fields and isolated wheezes was observed. The results of the laboratory tests showed elevated parameters of the inflammatory condition - high CPR 209 mg/l and leukocytosis 11 900/µl (Table 1). The ECG revealed sinus tachycardia 136/ min. A chest CT scan (Figure 3) with an angiogram was performed, demonstrating emphysematous, small-nodular and fibrous lesions, characteristic for COPD, and additionally, in the lower field of the right lung there was a focal lesion with a diameter of 48 mm. Spirometry showed very severe obstruction (FEV1 - 0.83l, 29% of predicted value, SR=-4.15). While in hospital, the patient reported falling down the stairs a few weeks earlier, resulting in a chest injury. After that accident, he suffered from hemoptysis for a few days. Core-needle biopsy under CT guidance was performed and samples for histopathology were taken. The material showed small fragments of the

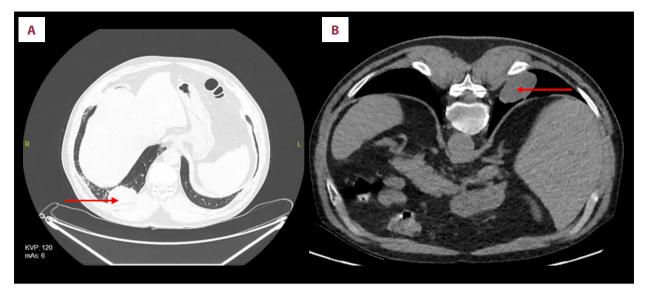


Figure 3. CT scans of the chest (A: pulmonary window, B: mediastinal window) of a patient with a hematoma. Red arrows denote a focal lesion with a diameter of 48 mm, which turned out to be a hematoma.

Table 1. Laboratory results - case 3.

Erythrocytes [3.9-5.7 mln/µl]	4.65
Hb [14-18 g/dl]	15.7
Leukocytes [4.1-10.9×10³/µl]	11.9
Neutrophiles [1.8-7.7×10³/µl]	8.89
Lymphocytes [1.0-4.5×10³/µl]	1.64
Monocytes [0-0.8×10³/µl]	1.22
Blood platelets [140-440×10³/µl]	237
CRP [0-5 mg/l]	209
Procalcitonin [0-0.5 ng/ml]	0.15
D-dimer [0-500 ng/ml (FEU)]	177
Fibrinogen [2.65-3.97 g/l]	8.08
Creatinine [0.8-1.4 mg/dl]	1.26
eGFR [ml/min/1.73 m ²]	56.9
NT-proBNP [0-125 pg/ml]	172.3

lung, including a few pulmonary alveoli with thickened interalveolar septa, with the presence of erythrocytes and hemosiderophages in the alveolar lumen, as well as a small fragment of fibrous connective tissue with chronic inflammatory infiltration. No neoplastic cells were observed, which supported the diagnosis of post-traumatic pleural hematoma.

Case 4

A 66-year-old patient with a history of hypertension was referred to the Pulmonology Clinic for diagnostic tests of a tumor in the left lung. The patient quit smoking 30 years ago, with approximately 10 pack-years in the medical history. On admission, the patient was in good condition but had dry cough and dyspnea on exertion. An examination revealed an audible vesicular murmur over the pulmonary fields, quieter over the whole left lung, and the lower limbs were swollen. A CT scan (Figure 4A) of the chest showed a solid, growing irregularly, a 10-15 cm extensive nodular and glandular infiltrate, remodeling the left lung, penetrating into the left upper and lower lobes, infiltrating the mediastinum and left hilum, filling the sub-spur space, and closing the left bronchus. Numerous cysts were detected in the liver, as well as a hypodense focus size 22 mm in the spleen, suspected of being the manifestation of metastases (Figure 4B). Spirometry showed an isolated decrease in FEV1 (1.04l, 51% of predicted value, SR=-3.03), with no signs of obstruction. Bronchofiberscopy was done, during which bronchial lavage was obtained for culture, and samples were taken from the pathologic mass located in the left main bronchus for histopathological examination. The material sampled from the left main bronchus contained diffused infiltrate from large B cells. The proliferation index Ki-67 was 70%. Based on the clinical and morphological findings, diffuse large B cell lymphoma was diagnosed. The patient was referred to the Hematology Ward for further treatment.

Discussion

An uncharacteristic clinical course and various changes detected through imaging tests in the course of many pulmonary diseases may raise the suspicion of lung cancer. Neacşu et al [14] discussed diagnoses which could initially mimic cancer: lung hamartoma with eosinophilic pneumonia, actinomycosis,

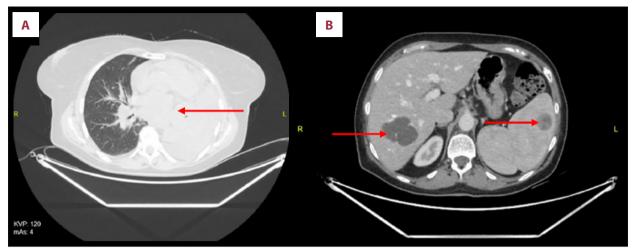


Figure 4. The CT scans of the chest (A: pulmonary window, B: mediastinal window) of a patient with diffused large B cell lymphoma.A) red arrow indicates a solid, extensive nodular and glandular infiltrate with the dimensions around 10-15 cm, remodeling the left lung. B) red arrow denotes lesions suspected of malignancy in the liver and spleen.

	Patient 1	Patient 2	Patient 3	Patient 4
History taking	Worse well-being, dry cough	Dry cough, loss of body weight	Dyspnea at rest and on exertion, productive cough	Dry cough, dyspnea on exertion
Physical examination	No deviations	No deviations	Weakened alveolar murmur over pulmonary fields, single wheezes	Swollen lower limbs, weaker alveolar murmurs over the left lung
Radiological image*	A nodular lesion with the diameter of about 9 cm infiltrating the lung hilum connecting to a nodular lesion containing calcifications, situated in the precardiac adipose tissue, which in turn connects to the thyroid tissue	A peripheral nodule measuring 24×13 mm, located in the right lung, and an enlarged lymph node size 12 mm in the right hilum	Emphysematous small- nodular and fibrous lesions. A focal lesion of 48 mm in diameter in the lower field of the left lung	A solid, growing irregularly, extensive nodular and glandular infiltrate size 148×102 mm, remodeling the left lung; cysts size 55×42 mm in the liver, a hypodense focal lesion in the spleen, size 25 mm
Histopathological examination**	The sampled material found to contain thyroid cells, but no neoplastic growth detected	Visible numerous epitheliocellular granulomas, some with central necrosis. No neoplastic changes were detected	Small fragments of the lung comprising a few pulmonary alveoli with thickened interalveolar septa, with the presence of erythrocytes and hemosiderinophages in the alveolar lumen	Diffused infiltrate from large B cells, proliferation index Ki-67 70%
Diagnosis	Ectopic thyroid tissue	Tuberculosis of the lungs	Post-traumatic pleural hematoma	Diffuse large cell B lymphoma

Table 2. Summary of the clinical, radiological and histopathological presentation of the cases.

* CT scan of the chest; ** core-needle biopsy material.

pulmonary aspergillosis, DIPNECH (diffuse idiopathic pulmonary neuroendocrine cell hyperplasia), cryptococcosis, and inflammatory myofibroblastic tumor of the lung. Many other papers provide descriptions of conditions that mimic lung cancer but do not originate from the respiratory system. For example, Yamada et al [15] reported a case of recurrence of ovarian cancer in the lungs, while Abdelghany et al [16] presented a case of a patient diagnosed with Ewing's sarcoma in the lung tissue. Minerva et al [17] discussed a case of a foreign body (a fragment of surgical thread left after earlier lobectomy) that caused a local inflammatory reaction, which in imagining tests strongly resembled a recurring lung cancer. In their review article, Furuya et al [18] characterized typical changes within the lung parenchyma visible in the chest CT scans appearing in the course of several diseases and difficult to differentiate from primary lung cancer. A number of conditions able to mimic lung cancer were discussed in the mentioned paper, such as hamartoma, pneumocytoma, IMT (inflammatory myofibroblastic tumor), tuberculoma, histoplasmoma, rounded atelectasis, amyloidosis, focal organizing pneumonia, lung abscess, focal pneumonia, and lymphoma in the lungs.

Following the assumption that a description of a specific case can best illustrate the difficulties in diagnosing and differentiating many health conditions from lung cancer, in this paper we reported cases that could have implicated lung cancer but were diagnosed as ectopic thyroid tissue, tuberculosis of the lungs, post-traumatic hematoma in the pleura, and diffused large B cell lymphoma (**Table 2**).

Ectopic Thyroid Tissue

The incidence of ectopic thyroid tissue is 1 per 100 000 to 300 000 persons in the general population. Due to the low incidence of this condition, there are no standard procedures for its diagnosis [19]. Initially, a large solid tumor visualized in a chest CT scan can suggest a cancerous lesion in the lung. Considering the radiological presentation, it is advisable to perform a core-needle biopsy and submit a sample to histopathological examination. Ectopic thyroid tissue can be found in many locations, including the tongue, mediastinum, trachea, lungs, aorta, and abdomen. It needs to be remembered that ectopic thyroid tissue can participate in the same processes as the thyroid gland located in the proper anatomical position. These processes include carcinogenesis, inflammation, and hyperplasia [20]. Having excluded the neoplastic character of the lesion, thyroid scintigraphy can be helpful in further diagnosis. In patients with ectopic thyroid tissue, it is also advisable to evaluate the functionality of the thyroid gland, because anomalies in the development of this organ can be a source of thyroid dysfunctions like hypothyroidism [21].

Tuberculosis of the Lungs

Both lung cancer and tuberculosis are significant challenges for the health care system all over the world. They show similarities in both clinical manifestations and sometimes in imaging tests. Both diseases can be characterized by a sudden body weight loss, fatigue, persistent cough, chest pains, and hemoptysis. One of the main factors influencing the incidence of infections with Mycobacterium bacteria is socio-economic status, and a subpopulation at a particularly high risk are the homeless [22]. Tumor-like lesions in the lungs giving rise to oncological concern can be a result of tuberculosis, especially when it forms tuberculomas [23]. Parenchymal granulomatous changes and changes in the form of irregular mass, consisting of lymph nodes enlarged in the course of TB, can also resemble the image of a lung cancer with metastases [24], and tuberculosis of the lungs and lung cancer can co-occur. Chronic inflammation, genomic alterations, and fibrosis are important factors that can promote carcinogenesis. A reverse reaction is the development of a neoplasm and treatment that can induce the reactivation of latent infection with tuberculosis [25,26]. Bhowmik et al [27] found a 1.64- to 6-fold higher incidence and risk of lung cancer in patients with tuberculosis in comparison with patients without this medical condition. The authors also remarked that both of these diseases are often concomitant and the more frequent occurrence of lung cancer, as well as the lowered immunity due to lung cancer, can predispose to infection with Mycobacterium tuberculosis. The tests that can significantly contribute to a successful differential diagnosis of the 2 diseases are microbiological tests and percutaneous core-needle biopsy of the lesion in the lung or USGguided transbronchial mediastinal biopsy [28,29]. It is even more important to be aware that the relationship is 2-sided. A more clinically dangerous situation is when lung cancer reveals characteristics of tuberculosis. Due to the tendency of lung adenocarcinoma to metastasize to the ribs and spine and the strong clinical and radiological similarity, it should be considered when diagnosing tuberculous spondylitis (Pott's disease) [30]. Khan et al emphasized the tendency to treat patients from tuberculosis endemic areas empirically despite a negative sputum smear, while metastatic disease should always be considered until a diagnosis is made. Referring to the former, a case of a patient from Indonesia (a country with a high incidence of TB) was initially diagnosed with tuberculosis and treated for 6 months, who ultimately turned out to have a Pancoast tumor [31].

Post-Traumatic Pleural Hematoma

A pleural hematoma in imaging tests can manifest as a tumor mass, often with accompanying bloody pleural effusion. The causes of a pleural hematoma can be post-traumatic, iatrogenic, or spontaneous. Lung cancer itself can be a cause of spontaneous pleural hematoma [32]. In the third case discussed in this article, the tumor lesion in the lung together with the history revealing a traumatic event attested to the diagnosis of a post-traumatic pleural hematoma. Bibo et al [33] described a case of a spontaneous pleural hematoma which appeared as the first sign of primary lung cancer. For this reason, when a pleural hematoma is detected, it is necessary to conduct an accurate and detailed diagnostic process to determine its etiology.

Diffuse Large B Cell Lymphoma

Primary lung cancer should also be differentiated from secondary cancer or other very rare primary neoplasms of the lungs. Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma [34]. In about 30% of cases, DLBCL originates from extranodal organs. Involvement of the kidneys, adrenal glands, ovaries, bone marrow, lungs, or pleura usually indicates disseminated disease, which is associated with a worse prognosis [35]. Primary diffuse large B cell lymphoma is extremely rare. To differentiate primary lung cancer from other lymphomas, it is necessary to conduct histopathological tests and an in-depth immunohistochemical analyses [36]. Due to the different methods of treatment, differential diagnosis should be made with utmost care. Moreover, it is worth noting that cases with coexisting metastatic lung adenocarcinoma and marginal B cell lymphoma presenting as pleural nodules have already been described [37]. Hong Zhi Alvin Ng et al presented a case of a very unusual B cell lymphoma with clinical and radiological image suggestive of metastatic lung cancer with a tumor thrombus in the pulmonary vein and left atrium [38]. The extraordinary cases mentioned above show the importance of accurate and fast differential diagnosis, as B cell lymphomas have much better prognosis than lung cancer if treatment is initiated without undue delay (generalized 5-year survival: 65% vs 20%) [39,40].

Limitations

Diagnostics of changes in the lung parenchyma is standardized, which enables effective and precise diagnosis of various pathologies, including cancer, inflammation, and vascular disorders. In most cases, the final diagnosis is achieved by biopsy, bronchoscopy, EBUS, or transthoracic lung biopsy. In the cases

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described here, such a procedure was implemented, obtaining an appropriate histopathological diagnosis in each case. The medical literature is full of case reports, but lung cancer remains the most common final diagnosis during the diagnosis of pulmonary lesions. A case report is a valuable educational tool and provides invaluable assistance to practitioners.

Conclusions

A wide array of pulmonary and non-pulmonary diseases demonstrate similar clinical and radiological presentation, mimicking primary lung cancers. Being aware of the spectrum of these conditions, understanding their pathological basis, and paying attention to clinical information facilitate making the correct diagnosis. Making the final diagnosis has a huge impact on the promptness and correctness of the treatment, which in turn determines the efficacy of therapy and the patient's prognosis in the long term. The tests which have a great conclusive importance are chest CT scans and percutaneous or transbronchial core-needle biopsy of the tumor-like lesion located in the lung [41].

Analysis of cases that shed light on specific difficulties in diagnosing changes in the lungs can be helpful in updating one's knowledge of potential pitfalls while making a diagnosis and differentiating the etiology of lung nodules with ambiguous or atypical symptoms. Careful differential diagnosis is equally important to avoid misinterpretation, which can alter the patient's therapy and eventually affect the timing of starting an appropriate treatment.

Department and Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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