

Case Report

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Calcified Nodules with Metastatic Dissemination to Multiple Organs and Systems: A Rare and Surprising Presentation of Primary Lung Adenocarcinoma



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Abstract

With increased use of computed tomography of the chest as a crucial diagnostic method, more lung injury began to be achieved in the early stages. One of the most important findings is the pulmonary nodules. Calcified pulmonary nodules are a group with a relatively narrow differential of diagnoses and will be discussed in this article. We report the case of a 46-year-old woman without prior disease who was evaluated in our emergency room with shortness of breath, cough and chest pain, both started two months ago. It progressed with progressive worsening of the condition in the last week. She denied weight loss, denied a fever, and denied drug abuse during that time. In the emergency room, the patient underwent chest radiography and chest tomography. Chest x-ray showed multiple radiodense lesions, some calcified, spread bilaterally over the lung fields. Chest tomography demonstrated multiple nodules and solid lung masses, most with calcifications, both of unknown etiology.

The initial diagnostic hypotheses were pulmonary tuberculosis, pulmonary neoplasia and pneumoconiosis. The initial support measures were performed, and the patient was admitted to our hospital for diagnostic investigation and treatment. During hospitalization, the patient was diagnosed with primary lung adenocarcinoma with calcified lesions and calcified metastatic lesions to organs and systems. Although common, it is of paramount importance to diagnose calcified pulmonary nodules and generally seek its etiology and cause, since these nodules can represent benign and or malignant lesions, having different conducts in the therapeutic approach.

Keywords: Tomography; Calcified Nodules; Primary Lung Cancer; Adenocarcinoma; Neoplasm Metastasis

Introduction

With the increase of computed tomography as a crucial diagnostic method, more pulmonary lesions started to be caught up at initial stages. One of the most important findings are pulmonary nodules. There are a lot of variations that might be considered to its evaluation, such as size, morphology and distribution. When it comes to morphology, there are three possible variations, solid pulmonary nodules, partly solid pulmonary nodules and ground glass pulmonary nodules. All of them can be calcified or not, and that's an important characteristic to guide the diagnosis [1].

Case Report

We report the case of a 46-year-old woman without prior disease who was evaluated in our emergency room with shortness of breath, cough and chest pain, both started two months ago. It progressed with progressive worsening of the condition in the last week. She denied weight loss, denied a

fever, and denied drug abuse during that time. In the emergency room, the patient underwent chest radiography and chest tomography. Chest x-ray (Figure 1) showed multiple radiodense lesions, some calcified, spread bilaterally over the lung fields. The initial diagnostic hypotheses were pulmonary tuberculosis, pulmonary neoplasia and pneumoconiosis. The initial support measures were performed, and the patient was admitted to our hospital for diagnostic investigation and treatment. During the hospitalization, a complete anamnesis was performed that discarded a history of exposure to potential pathological particles. Laboratory tests were within normal limits and tuberculosis research was negative. The patient underwent further imaging tests, such as neck, thorax and total abdomen tomography, and performed a battery of laboratory tests, including tuberculosis research.



Figure 1: Chest X-ray in PA showing multiple radiodense lesions, some calcified, sparsely scattered across the lung fields bilaterally.



Figure 2: Axial tomography of the neck (soft tissue window) demonstrating an expansive mass of inaccurate limits and with gross calcifications (red arrows). This mass is located in the right supraclavicular / cervical region and is suggestive of secondary involvement.

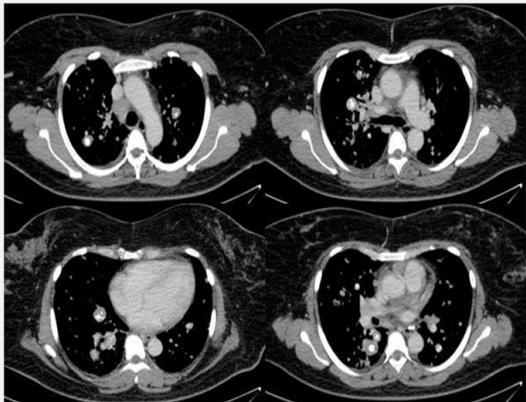


Figure 3: Chest tomography in axial section (window mediastinum) showing few solid lesions, some calcified, scattered in the lung fields bilaterally.

The tomography of the neck (Figure 2) showed an expansive mass of imprecise limits and with gross calcifications in its interior. This mass is located in the right supraclavicular / cervical region and is suspected of secondary involvement. Chest tomography (Figures 3 & 4) shower some nodules and solid lung masses, most with calcifications, both of unknown etiology. Calcified lymph nodes on both sides of the neck and mediastinum were also observed. Tomography of the abdomen

(Figure 5) demonstrated a nodular thickening in the adrenal glands, probably due to secondary involvement. Other abdominal organs with no apparent signs of injury. No changes were found in breast, thyroid, and bone. Neoplasia and pneumoconiosis continued as the main hypotheses in the differential diagnoses after this new evaluation.

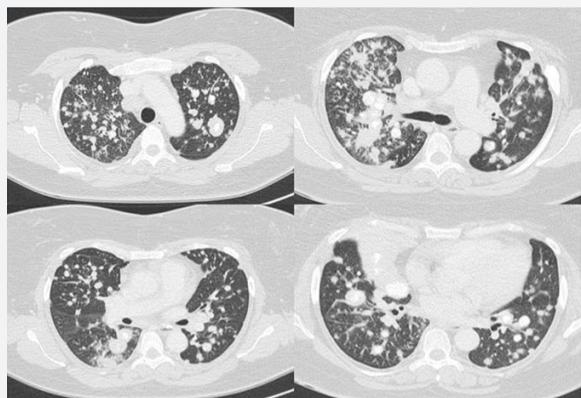


Figure 4: Chest tomography in axial section (window lung) showing few solid lesions, some calcified, scattered in the lung fields bilaterally.



Figure 5: Tomography of the abdomen in axial section (soft tissue window) showing adrenals affected by thickening, sometimes nodular, lesions suggestive of secondary involvement.

The medical team decided to continue the diagnostic investigation by performing a biopsy of the lesion in the supraclavicular / right cervical region and sent the collected material to the anatomopathological. The anatomopathological result (Figure 6) showed acinar structures in the extracted lesion. An immunohistochemical study (Figure 6) was requested, which resulted in positive cytokeratin 7 (CK-7); Positive Thyroid Transcription Factor 1 (TTF-1); E-cadherin positive; Positive Epithelial Membrane Antigen (EMA); other factors, such as thyroglobulin, chromogranin, CK 5/6, Ca 125, CK 20 estrogen receptor, progesterone receptor and WT-1 were all negative. This immunoexpressed profile is highly suggestive of primary lung cancer [2-4], which was considered the final diagnosis due to the lack of findings in other organs. The chemotherapy regimen for primary lung adenocarcinoma was started and the patient presented progression of the disease with low response to treatment. About three months after diagnosis, a new chest tomography (Figures 7 & 8) revealed an increase in the number

and size of lung lesions. In addition, a computed tomography scan of the skull was performed to assess a complaint and a symptom of the patient's visual turbidity in the right eye. Cranial tomography (Figure 9) showed an amorphous solid lesion within the right eyeball, which evolved from partial involvement to total vitreous humor. No extra-axial or intra-axial cranial changes were found. This eyeball injury was considered as secondary involvement. The clinical team decided to keep the chemotherapy regimen current and the patient had progressive clinical worsening. Currently, the patient is being treated with another chemotherapy regimen for primary lung adenocarcinoma, with a low clinical response, making this case challenging and atypical.

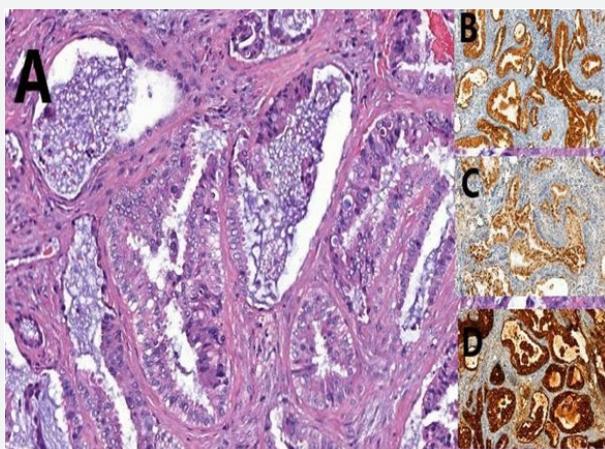


Figure 6: Represents histological sections in Hematoxylin and eosin staining (H & E) and immunohistochemical reactions (IHC) in the 100x increase of the cervical lymph node. A- Infiltration by adenocarcinoma consisting of branched and epithelial-coated acini with loss of polarization and intense cellular atypia. B - Demonstrate the IHC reaction for the TTF1 positive antibody in the nucleus. C - Demonstrate the IHC reaction for the positive CK7 antibody in the cytoplasm and in the cytoplasmic membrane. D - Epithelial Membrane Antigen (EMA) positive in the cytoplasm and in the cytoplasmic membrane.

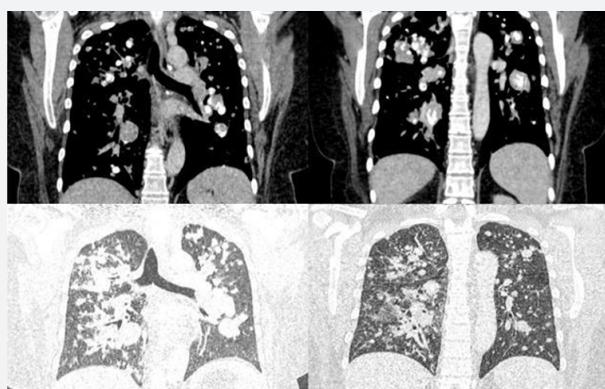


Figure 7: Chest tomography in coronal section (window mediastinum and lung) showing multiple masses and solid nodules, some calcified, scattered in the lung fields bilaterally. Note the increase in size and number of lung lesions compared to computed tomography three months earlier.

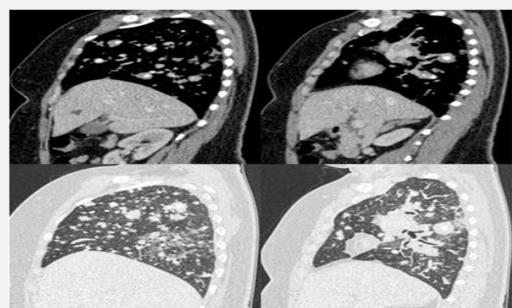


Figure 8: Chest tomography in sagittal section (window mediastinum and lung) showing multiple masses and solid nodules, some calcified, scattered in the lung fields bilaterally. Note the increase in size and number of lung lesions compared to computed tomography three months earlier.

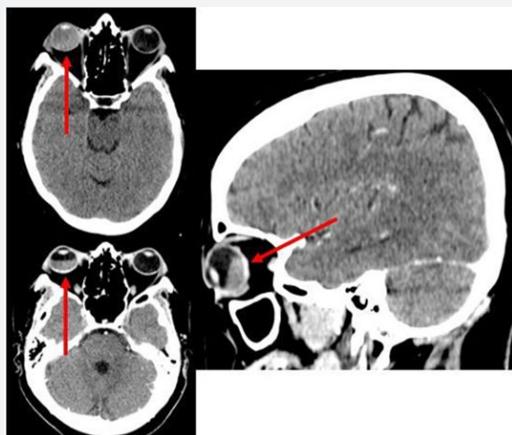


Figure 9: Skull tomography in axial and sagittal sections (soft tissue window) showing an amorphous solid lesion inside the right eyeball, a lesion suggestive of secondary involvement (red arrows).

Discussion

Calcified pulmonary nodules are a group with a relatively narrow differential [5]. Usually central, diffuse, laminated or popcorn calcifications are benign patterns [6]. These types can be seen in granulomatous disease and hamartomas. The most common cause of nodule calcification is granuloma formation in response to a healed infection, with residual aspect. All other patterns of calcification should be considered, at least, suspicious. However, there is an exception. If the patient is known to have a primary tumor, a diffuse calcification, for example, may be seen in osteosarcoma pulmonary metastasis [7]. Other examples are central and popcorn patterns, which also may be seen in patients with GI-tumors and patients who already passed throughout chemotherapy. Occupational diseases, also known as pneumoconioses, are a differential that need to be considered, which explains why is so important to know the patients background history of work [6]. Silicosis is associated with nodal egg-shell calcification and multiple small densely calcified nodules that are upper lobe predominant. Coal worker's

pneumoconiosis may present the same pattern of silicosis, but with smaller nodules, and minimal symptoms [8].

Just as previously said, patients with known history of primary cancer showing multiple calcified pulmonary nodules at CT scan, need to be considered with a high chance of having calcified pulmonary metastasis. Typically, there are a variety of mechanisms that cause calcification in metastasis, such as bone formation in tumors osteoid origin, calcification and ossification of tumor cartilage, dystrophic calcification and ossification of tumor cartilage and dystrophic calcification and mucoid calcification [7]. The spectrum of primary malignancies that can cause calcification of metastatic nodules, includes sarcomas, such as osteosarcoma, chondrosarcoma and synovial sarcoma; mucinous type carcinomas, including colon carcinomas, ovarian cancers and breast cancer; medullary thyroid carcinoma; giant cell tumor of the bone and treated metastatic choriocarcinoma [7]. Primary adenocarcinoma of the lung is the most frequent histological type of lung cancer (around 40% of the cases), being also the most diagnosed one in non-smokers, besides more seen in smokers. Histologically it is classified as a non-small cell carcinoma and is a malignant tumor that can be associated with mucin production, which, in some cases, develops mucoid calcification [5-15].

In 2011 a new classification for adenocarcinoma of the lung was introduced by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS), dividing its types in: preinvasive adenocarcinoma lesions; minimally invasive adenocarcinoma and invasive adenocarcinoma. One of the variants of this least one type is the invasive mucinous adenocarcinoma (formerly mucinous BAC), which is more likely to be multicentric multilobar, and may show bilateral lung involvement [12], indicating aerogenous spread [13], tending to have a worse prognosis than non-mucinous types.

The anatomopathological report of the biopsied cervical lymph node was infiltration by adenocarcinoma. The sample was submitted to a complementary immunohistochemical examination, which revealed a highly suggestive pattern of primary adenocarcinoma of the lungs: CK 7+, TTF-1 +, and CK 20 -, rejecting the hypothesis of an extrapulmonary primary site with specificity above 98% [2-4]. Other sensitive markers were positive in the sample, such as E-cadherin and epithelial membrane antigen (EMA), which corroborate the diagnosis of carcinoma. Markers such as WT1; Ca 125; Thyroglobulin; Progesterone and Estrogen receptors; CK 5/6 and Chromogranin were negative in the sample, corroborating the findings of previous complementary tests, negative for ovarian, thyroid, breast, gastrointestinal tract and neuroendocrine tumors.

Conclusion

There are not many case reports in the literature showing primary lung adenocarcinomas with calcified aspect associated

with metastases. In this case, in addition to the unusual pattern, the secondary involvement of the lung, adrenal and right orbit of the patient (metastasis to the orbits may present as primary site the lungs in up to 23% of the cases) [14]. Such diversity of findings led the medical team to first rule out non-neoplastic hypotheses of calcified pulmonary nodules. After confirming the carcinomatous pattern, all the possible primary sites of extrapulmonary adenocarcinomas were investigated, which did not show relevant alterations. With the result of the anatomopathological and immunohistochemical tests, the diagnosis was closed for this challenging case of pulmonary primary adenocarcinoma of aggressive behavior and calcified pattern.

This case report is important for radiologists and the medical community in general, as it demonstrates through CT scan an infrequent spectrum of lung adenocarcinoma, presenting as lung nodules and calcified metastases.

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