

## Pulmonary nodules: a challenging diagnosis during the follow up of cancer patients

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### ABSTRACT

Pulmonary nodules (PN), frequently found on imaging studies, represent a diagnostic challenge during the follow up of cancer patients. However, published data regarding investigation of PNs incidentally found on chest imaging is scarce. The PN may be present at the time of cancer diagnosis, or arise during the treatment or follow-up periods. In the context of the oncologic patient these lesions are quite invariably considered as metastases, what impacts directly on patients' treatment and prognosis. The present study reports 2 cases of pulmonary nodules found in two patients already diagnosed with cancer. Case 1 referred to a woman with squamous cell carcinoma and two pulmonary nodules, and in case 2 the patient was diagnosed with duodenal adenocarcinoma. Both patients were submitted to pulmonary biopsies before the oncologic treatment. In both cases the nodules were of infectious origin, what changed significantly the neoplasia staging and the oncologic treatment intention. The authors performed a literature review as well as a discussion about the management of PN in cancer patients.

### Keywords

Multiple Pulmonary Nodules, Neoplasms, Tuberculosis, Biopsy.

### CASE 1

A 68-year-old female patient complaining of vaginal itching and pain presented a vulvar mass, with vaginal invasion at gynecological examination. She denied tobacco smoking. Tumoral biopsy diagnosed vulvar squamous cell carcinoma. Staging exams included pelvic MRI, abdominal and thoracic computed tomography (CT), revealed two spiculated irregular lung nodules (Figure 1), establishing the diagnosis of a T3 N0 M1 (lung), stage IV vulvar carcinoma. As the patient did not present the typical and expected pelvic and/or inguinal lymph node involvement, we decided

to biopsy the lung nodules, to confirm the diagnosis of metastasis.

Thus, two nodules were biopsied, revealing the presence of chronic inflammatory reaction with granulomas (Figure 2A) and the Ziehl-Neelsen staining was positive for mycobacteria, consistent with the diagnosis of pulmonary tuberculosis (Figure 2B). No evidence of neoplasia was found in the biopsied specimen.

After the diagnosis of pulmonary tuberculous nodules, the patient was referred to gynecological

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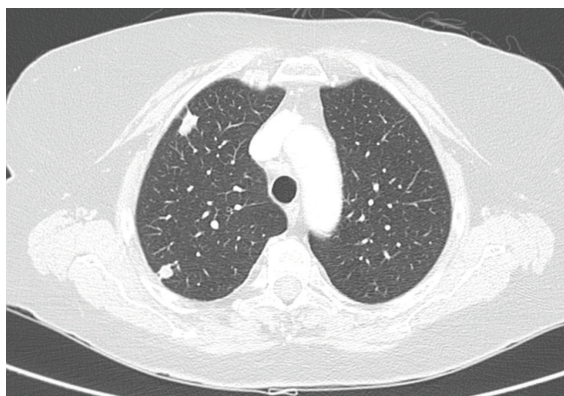
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surgery, with curative intention, as a T3 N0 M0 vulvar cancer, and started the antituberculous standard treatment.

## CASE 2

A 73-year-old female patient, previously diagnosed with diabetes mellitus and hypertension, sought medical attention because of jaundice and abdominal pain. Abdominal CT scan revealed a periampullar mass measuring 4,7cm at its longest axis and endoscopy confirmed a necrotic lesion in the duodenal papilla. Biopsy was performed and revealed adenocarcinoma,



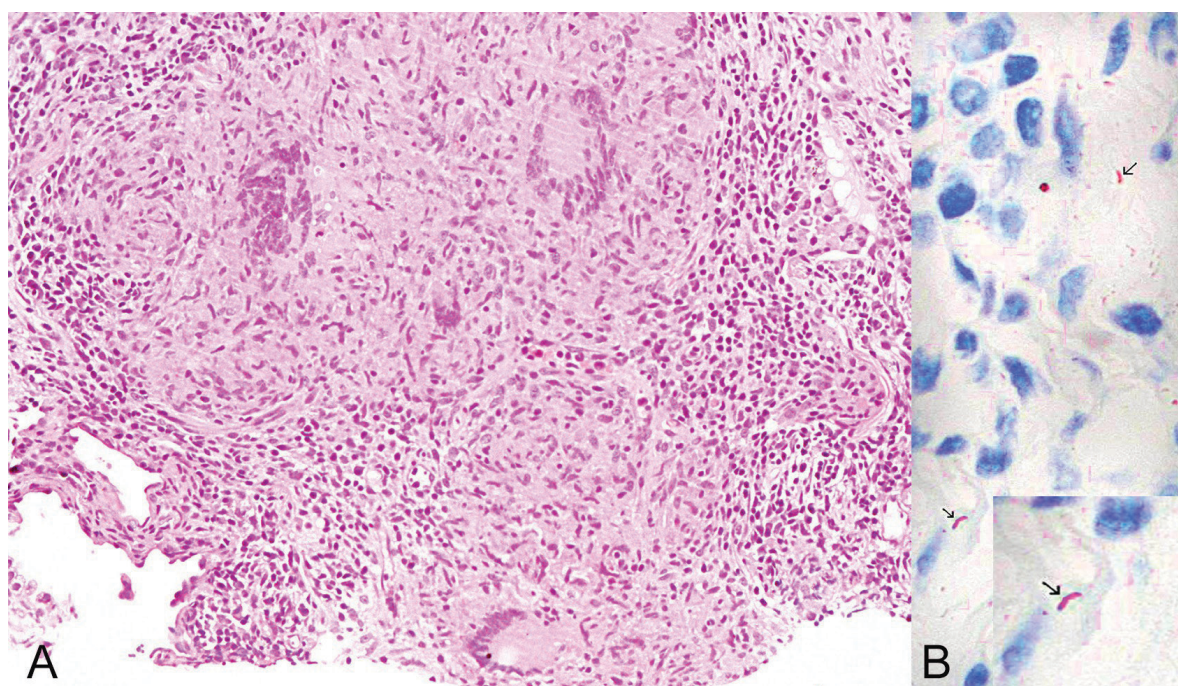
**Figure 1.** Thoracic computed tomography showing subpleural spiculated nodules.

consistent with duodenal origin. Staging CTs revealed bilateral pulmonary nodules (1,5cm), raising the suspicion of metastatic disease (Figure 3). Lung biopsies (2 nodules) were performed, revealing chronic inflammatory granulomatous reaction with caseous necrosis (Figure 4). Ziehl-Neelsen staining was positive for acid fast bacilli, consistent with pulmonary tuberculosis. She started on anti tuberculous treatment, and was referred to surgery with the diagnosis of T4 N0 M0 duodenal adenocarcinoma.

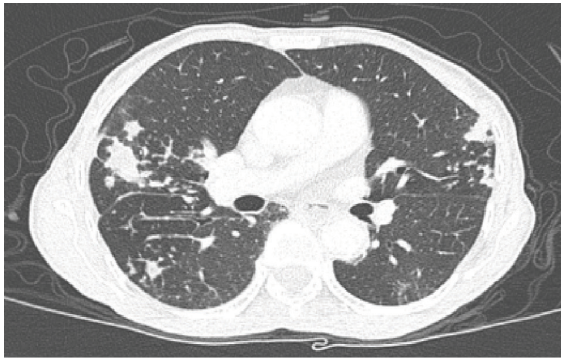
## DISCUSSION

The diagnosis of pulmonary nodules in cancer patients, whether metastatic or localized disease, is crucial to determine the best therapeutic approach, ranging from curative intention (non-metastatic) to palliative (metastatic) in most cases. Both cases reported herein presented pulmonary nodules concomitantly with nonpulmonary tumors, what would be presumably interpreted as metastatic disease.

A literature review was performed, using the keywords "tuberculosis and pulmonary nodules"; "tuberculosis and cancer" and "pulmonary nodules and cancer" on the MEDLINE (PUBMED) and TRIP databases. We sought for publications (including case reports and review articles) which described the



**Figure 2.** Photomicrography of the pulmonary nodule biopsy. **A** - Presence of granulomas with giant cells (HE, 100X); **B** - Presence of acid- fast bacilli small arrows, in detail in the inset (Ziehl-Neelsen, 1000X).



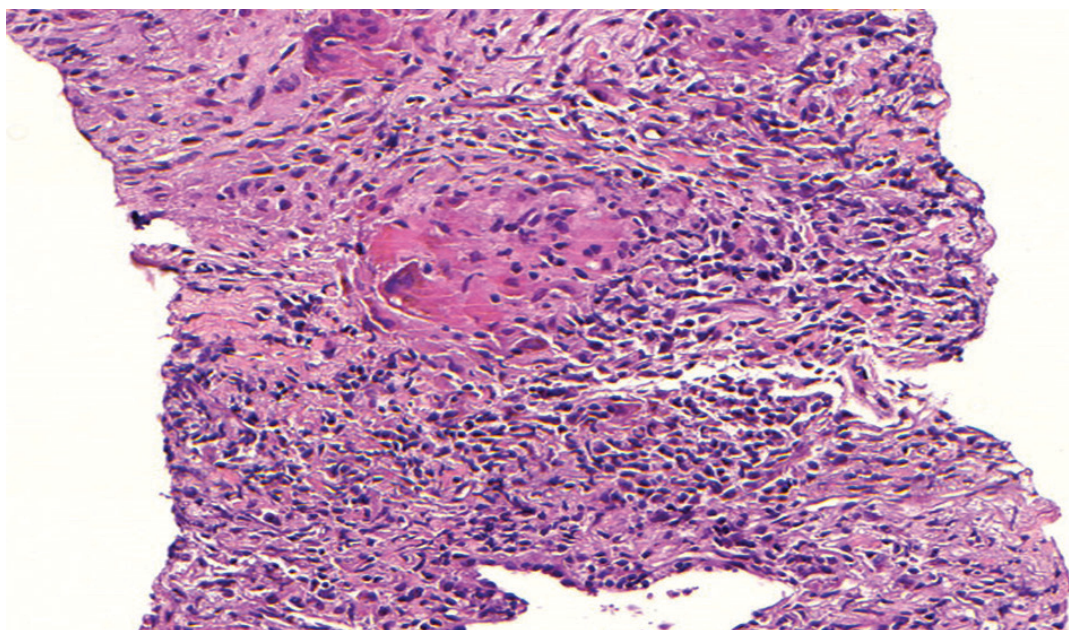
**Figure 3.** Thoracic computed tomography showing multiple bilateral scattered pulmonary nodules, some of them confluent and spiculated.

diagnosis and prevalence of tuberculosis in cancer patients, and we did not define a specific period of time for the articles included in the present review.

Pulmonary nodules (PNs) are frequently encountered on imaging studies, and represent a diagnostic challenge.<sup>1</sup> The range of differentials is wide, including metastases, primary lung cancer, infectious diseases, scar tissue, anthracosis and others. Among patients already diagnosed with cancer, there is scarce data regarding the optimal investigation of PNs. In a series of 800 patients with solitary lung nodules and a previous diagnosis of extra pulmonary cancer, submitted to lung biopsy, resection or autopsy, Cahan et al.<sup>2</sup> found approximately 500 primary lung cancers, and 11 benign lesions. In 2006, Khokhar et al.<sup>3</sup> published

the evaluation of the records from 151 patients with extrapulmonary cancers and non-calcified pulmonary nodules, finding 42% of malignant nodules, and 58% of benign lesions. In this study, 50% of the patients who were considered to have a malignant nodule had lung cancers (new primary cancer). In a study with 1.104 patients submitted to PN resection, Mery et al.<sup>4</sup> observed a 63% percent rate of malignancy in 337 patients with previous cancer history. These results, despite their methodological considerations (retrospective studies), suggest a high incidence of secondary malignancies among patients with extra pulmonary cancers. Albeit, not infrequently, some of the lung nodules may present as non-neoplastic lesions, such as scar tissue, sarcoidosis, or infections, like the cases presented herein.

The decision of performing a pulmonary nodule biopsy in a cancer patient can not be guided by robust evidence due to data scarcity. Although biopsy is the best way to obtain a tissue sample for analysis and to reach an accurate diagnosis, complications associated with the procedure might occur, and this must be taken into account when requesting a diagnostic PN biopsy. Also, we have to consider the costs involved in the procedure, since it requires sophisticated imaging studies, appropriate equipment, a trained radiologist and hospital facilities prepared to deal with procedure's associated complications. The evaluation on the likelihood of a PN being a metastasis or not should take into account: the primary site of the cancer,



**Figure 4.** Photomicrograph of the lung biopsy showing chronic granulomatous inflammatory process.

previous history of tobacco exposure, the presence of concomitant other sites of metastatic disease, the size of the nodule, its evolution over time (nodules which are progressively increasing in size are very suspicious for malignancy), and the aspect on imaging studies (irregular nodules, with a necrotic center and cavitation suggest cancer).<sup>1</sup>

In the Case 1, for example, patient had no history of tobacco smoking and the presence of lung metastasis would not be expected in a vulvar squamous cell cancer without regional lymph nodes involvement. Given the possibility of a non-metastatic pulmonary disease, we performed the biopsy. In Case 2 we also found odd the presence of a marked pulmonary involvement in the absence of hepatic and other evident regional lymph nodes enlargement. Biopsy results changed our approach from palliative (metastatic disease) to curative (local disease) treatment.

We strongly consider the importance and therefore recommend to raise the suspicion of a non-malignant origin of a PN in a cancer patient. Given the impossibility to accurately estimate the origin of a PN based solely on imaging studies, and the relative safety of the pulmonary

biopsy,<sup>2-4</sup> we recognize the lung biopsy as an important tool for therapeutics guidance.

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