


CASE REPORT

Laterocervical lymph node metastases from suspected thyroidal primary site that turned out to be metastases of lung cancer: A case report

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Key Clinical Message

Incidental sonographic discovery of thyroid nodules is an increasingly common event in clinical practice. Less frequently, patients with cytological benign thyroid nodules have suspicious cervical lymph nodes detected by ultrasound examination or by cytological exam. Here, we discuss an intriguing case of cervical lymph node metastasis with a probable thyroid origin in a 65-year-old asymptomatic male smoker. He underwent thyroidectomy and unilateral cervical lymphadenectomy. Despite a negative chest X-ray, the postoperative histological examination revealed that the lymph node metastasis was actually from a lung carcinoma. Metastatic lesions in cervical lymph nodes from non-thyroidal origins must be excluded when evaluating lesions in the region, especially when thyroid nodules subjected to fine needle aspiration biopsy yield negative results, or lymph node cytological evaluations are inconsistent with thyroid cytological findings and sonographic features. Thyroid and lung adenocarcinomas share some epithelial and mesenchymal markers. Thyroglobulin helps differentiate primary thyroid tumors from lung ones, but in cases of poor differentiation, distinguishing metastatic lesions in the thyroid gland can be challenging. Lung cancer (LC) is the leading cause of cancer mortality worldwide, and survival rates have only marginally improved over the last several decades. The ongoing clinical challenge is detecting LC at earlier stages of the disease.

KEYWORDS

case report, lung adenocarcinoma, lung cancer, non-thyroidal cervical lymph node metastases, thyroid cancer

JEL CLASSIFICATION

General surgery

Chiara Scorziello and Maria Carola Borcea contributed equally.

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1 | INTRODUCTION

Cervical lymphadenopathy is a common finding, caused by inflammatory or infectious diseases and neoplasm, both primary and metastatic. Cervical lymphadenopathies of unknown primary are a special challenge.¹ Most of them come from primary cancer of the head and neck, but sometimes the primary is in a remote site.² These cases pose a diagnostic challenge, especially when the cytology from the enlarged nodes does not clearly suggest a site of origin. In this report, we present a case of an asymptomatic man with cervical lymph node metastasis, suspected to be from a thyroidal primary site during an ultrasound screening program. The final pathology, however, revealed metastasis from lung adenocarcinoma. Early detection of lung cancer (LC) before symptoms or discomfort arise is increasingly important, and it remains a challenge. This case highlights the need to double-check the primary diagnostic hypothesis when findings are not fully concordant.

2 | CASE REPORT

A 65-year-old man was referred to our Department of Surgery with cervical lymph node metastasis of likely thyroidal origin detected during an ultrasound screening program. In particular, the ultrasound examination indicated the presence of an enlarged thyroid gland with an increased echogenicity and a homogeneous echoic texture. It also reported a mixed polylobate isthmic nodule (13.5×7.3×14.2 mm) with signs of peripheral vascularization pattern two and two solid nodules in the left lobe; the smaller one (3.1×4.1×3.5 mm) had irregular margins

and internal and peripheral hyperechoic spots. According to ACR White Paper 2017, the isthmic (mixed cystic and solid composition, iso-echogenicity, well-defined margins) and the bigger left lobe nodule (solid composition, well-defined margins and iso-echogenicity) were classified as TR3, mildly suspicious, while the smaller left lobe nodule was classified as TR4, moderately suspicious, presenting a total score of 5 (2 points for solid composition, 2 points for irregular margins, 1 point for hyperechoic spots).³ In the left lateral cervical area, at Level IV, lower internal jugular (deep cervical) chain, lateral to the vessels, a lymph node with a mixed echo structure of 17.6×21.4×27.7 mm and caudally a block of nodes that measured a total of 9.8×19.4×17.5 mm (Figures 1 and 2). A fine needle aspiration biopsy (FNAB) guided by ultrasound of suspected lymph nodes showed metastasis of carcinoma morphologically compatible with a thyroid differentiated tumor, even though the TR4 left lobe nodule was found to be non-neoplastic THY2.⁴ Thyroid nodule cytology showed abundant colloid background, macrophages, and numerous flaps and/or aggregates of thyrocytes free of significant atypia, nodule defined as hyperplastic. The cytology findings of the lymph nodes showed plurinucleate macrophages, lymphocytes, and numerous irregular aggregates, sometimes papillary, of cells with enlarged nuclei, round-oval shaped, nucleated, optically clear, with longitudinal incisions and occasional pseudo-inclusions. The cytology of the nodes was consistent with the hypothesis of a metastasis from a differentiated thyroid tumor. Hence, despite the cytology of the larger nodule being negative for cancer, the possibility of papillary carcinoma could not be ruled out, especially when considering the suspicious findings of the ultrasound and the ACR TIRADS score. The patient's past medical history included arterial

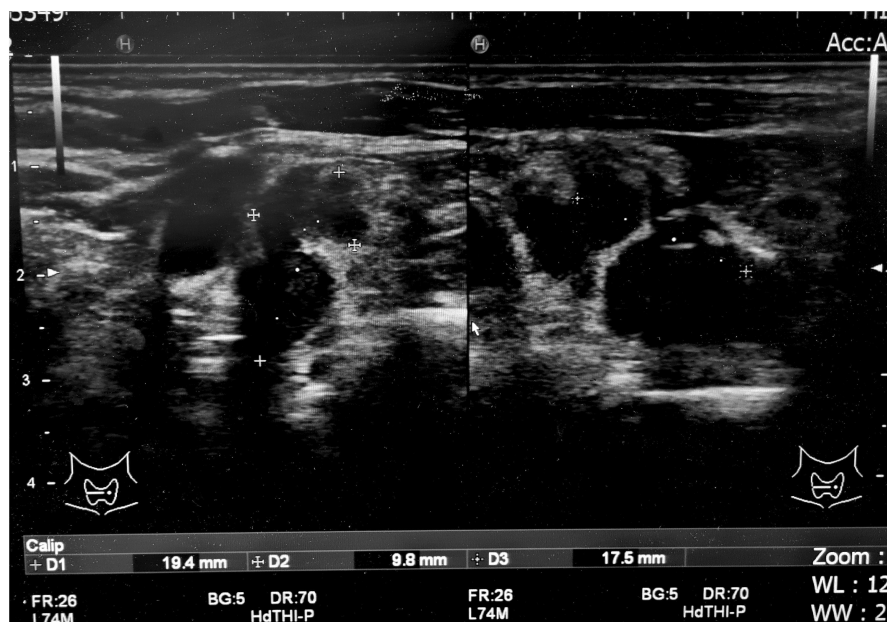


FIGURE 1 Ultrasound image of suspected IV cervical level lymph node block measuring 9.0×19.4×17.6 millimeters.

hypertension treated with selective beta blocker, symptomatic gastroesophageal reflux disease in treatment with omeprazole and, and most notably, a chronic obstructive

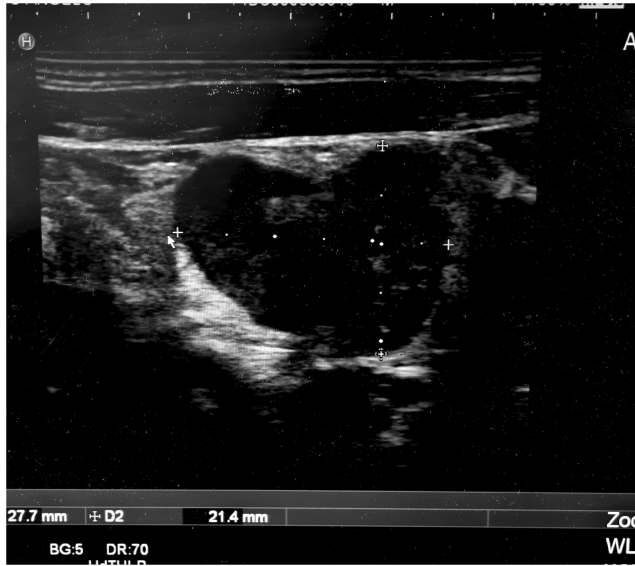


FIGURE 2 Ultrasound image of lower internal jugular chain (deep cervical) lymph node block, measuring $17.6 \times 21.4 \times 27.7$ mm.

pulmonary disease with mild obstructive deficit confirmed by a spirometry test. The patient reported being a heavy smoker: two packs a day for 30 years. Chest X-ray was normal.

After obtaining informed consent, the patient agreed to undergo surgery. He underwent total thyroidectomy, central compartment lymph node dissection and left lateral cervical lymphadenectomy (Levels II–IV).

Histologically, the lymph nodes showed an effacement of the normal architecture by a proliferation of tumor cells arranged in irregular shaped glands (**Figure 3A**). Under high magnification, the tumor cells showed an enlarged nuclei, large nucleoli, and abundant cytoplasm in some cells (**Figure 3B**). Based on morphology, a diagnosis of metastatic adenocarcinoma was hypothesized. The positive immunostains for CK7, TTF-1 and Napsin A (**Figure 3C–E**) and the negative stains for PAX8 and thyroglobulin were consistent with the lung origin of the neoplasm and excluded a thyroid primitivity definitely. PD-L1 (SP263) expression by the tumor proportion score as a predictor of response to immune checkpoint inhibitor therapy was assessed⁵ and resulted in a value of 40% (**Figure 3F**). Immunohistochemistry for ALK and ROS1

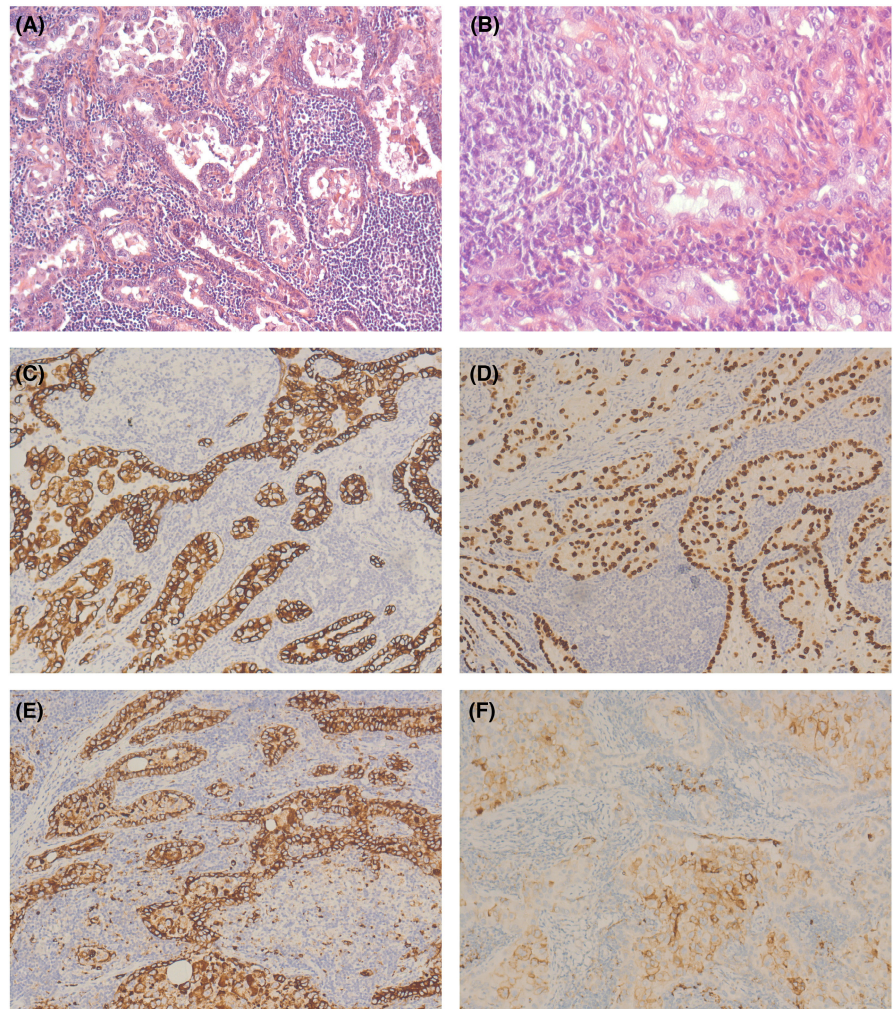


FIGURE 3 Representative low-(A) and high-(B) power magnification of the adenocarcinoma metastatic to one of the lymph nodes. Representative images of sections immunostained for CK7, TTF-1, Napsin A and PD-L1 are shown in C, D, E, and F, respectively.

was also performed, with a negative result. The molecular assay detected a KRAS G12A mutation and the absence of mutation in BRAF and EGFR genes.

The pathology of the thyroid did not reveal any neoplasm. Histological examination of the gland showed multinodular hyperplasia with aspects of colloid-cystic involution and adenomatoid nodules with micro-follicular growth. Whole PET-CT total-body scan showed an abnormal uptake in left supraclavicular area (target lesion QClear SUVmax 5.0), in all the mediastinal hilum lymphatic stations, in the right para tracheal area (QClear SUVmax 5.2), at the emergence of the periaortic vessels (QClear SUVmax 3.1) (Figure 4), precarenal (QClear SUVmax 6.3) and subcarinal area (QClear SUVmax 7.1), right hilar (QClear SUVmax 5.5) and bilateral perihilar vessels (QClear SUVmax 7.9) (Figure 5). Concomitant large amount of lymph node tissue was found in the left perihilar posterior to the ipsilateral main bronchus (QClear SUVmax 8.5) (Figure 6). These findings were consistent with metastatic lesions.

The PET body scan also showed a pathological uptake in the thyroid bed. In the lung area, there were pseudo nodular formations in bilateral apical areas (QClear SUVmax 2.1), and a cavitory lesion in left basal area of 2.5 cm (QClear SUVmax 2.1) (Figure 7). In the skeletal area, hypermetabolic foci were observed in correspondence with the transverse process of D2 (QClear SUVmax 5.9) and the sternum (QClear SUVmax 6.8). No evidence of suspected foci in hepatic, splenic, pancreatic,

and adrenal site or in pelvic and peritoneal site. Figure 8 shows the patient's negative chest X-ray scan before performing the whole-body PET-CT and before starting any treatment. The lung tumor was classified Stage IV (T1cN3) according to the 2017 Union for International Cancer Control (UICC) staging.⁶ In a multidisciplinary team meeting, the tumor was deemed ineligible for surgery. One month later, the patient was administered chemotherapy, using first-line carboplatin–paclitaxel in a single shot, followed by immunotherapy with a combination of ipilimumab and nivolumab, as stated in the CheckMate 9LA Study⁷ for patients with advanced non-small-cell LC. The patient completed seven therapy cycles. Last PET-TC (January 2023) showed total regression of pulmonary findings bilaterally but persistence of left perihilar lymphadenopathy: partial response to current therapy. Four months later the patient is still alive and asymptomatic.

3 | DISCUSSION

This case is a good example of “confirmation bias”.⁷ The negative cytology on the FNAB of the thyroid nodule should have induced to deepen the diagnostic workup, despite the US finding, considering a second hypothesis of metastasis from a remote site. Most malignant lymphadenopathy in the neck represent lymphomas or metastases from head and neck primary tumors, like thyroid cancer,

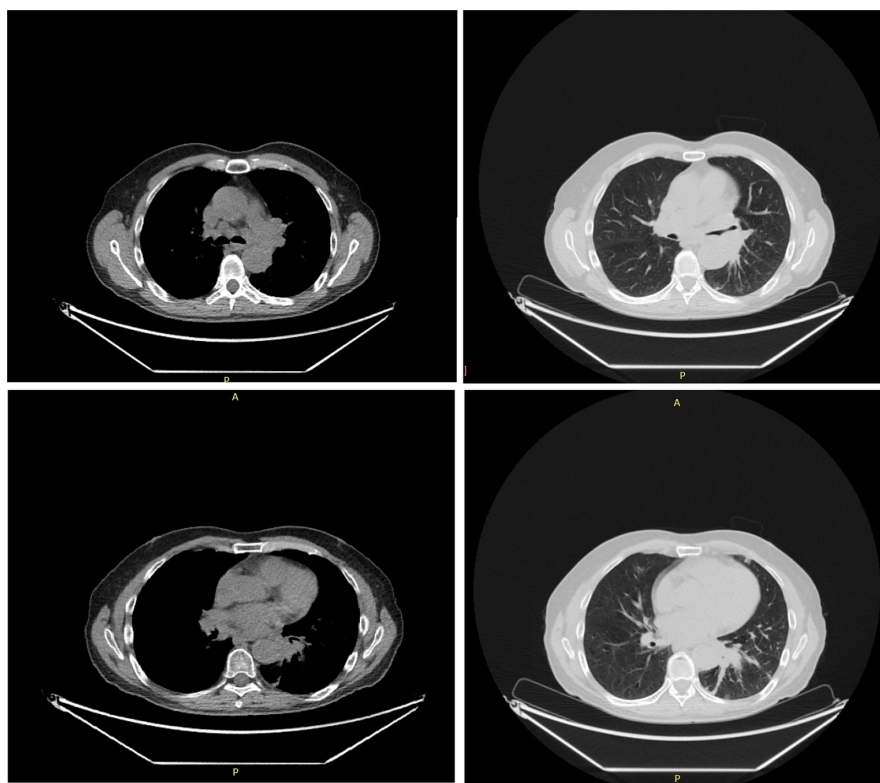


FIGURE 4 CT scan showing large amount of lymph node tissue in all the mediastinal hilum lymphatic stations, in the right paratracheal site, to the emergence of the periaortic vessels.

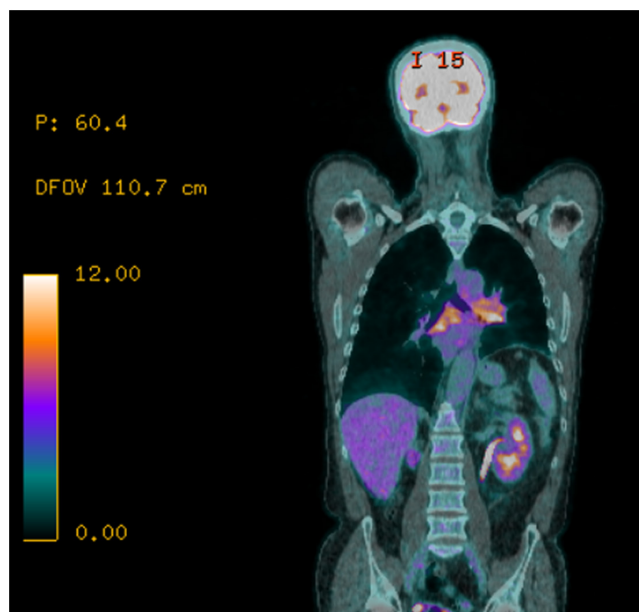


FIGURE 5 PET scan showing pathological uptake in precarenal and subcarinal area, right hilar and bilateral perihilar vessels.

and occasionally, metastatic disease from remote sites presents as cervical lymphadenopathy.¹

Carcinomas of unknown primary site are a heterogeneous group of metastatic diseases in which the site of the primary tumor is not identified after clinical evaluation and diagnostic investigation.

The most frequent sign of disease onset found is cervical lymph node enlargement (94%).⁸ Treatment of cervical tumors from unknown primary focus remains a diagnostic and therapeutic challenge. In general, primary lesion below the clavicle has metastasis in supraclavicular nodes while primary lesion above the clavicle has cervical nodes at other levels.⁹ When the metastatic lymph node is in Levels I–III, it is most likely that the site of the primary tumor is in the cervical-cephalic region. In the case involvement of Levels IV and V the site of the primary tumor is, located above the clavicles.

Papillary thyroid carcinoma can develop with lymph node metastasis in 30% of cases, even at the time of diagnosis.¹⁰ The most common remote primary tumors associated with neck lymph node metastases include cancers of the breast, lung, kidney, cervix, and testis.

The frequency of cervical lymph node involvement in patients with LC ranges from 1.5% to 32%.¹¹ LC represents the first cause of death for cancer in men and the third in women.¹² Despite advances in diagnosis and treatment, 5-year survival is 15%.¹³ The main determinant of survival is the degree of tumor extension at the time of diagnosis. LC has its maximum incidence between the ages of 55 and 65 and a clear relationship with tobacco habit.¹⁴ More

than 90% of lung neoplasm are malignant tumors and, even today, this neoplasm remains with a poor prognosis. Adenocarcinoma is the most frequent histotype and is part of peripheral lung carcinomas.¹⁵ At the time of diagnosis, most patients have an advanced form and only in 20% of cases the disease is localized (often incidental diagnosis rather than related to symptoms). Unfortunately, like in our case report, most patients arrive at the diagnosis with a neoplasm already at an advanced stage, with metastasis, also because in its initial stages the disease does not show evident signs of its presence. This means that many of the patients are not surgical candidates.

Chest X-ray is the first diagnostic investigation required in the suspicion of pulmonary pathology.¹⁶ Nevertheless, in almost one out of four patients with symptoms of LC, the report of chest X-rays is not suggestive of cancer. The sensitivity estimates for chest X-ray spans from 76.8% (95% CI=64.5 to 84.2%) to 79.7% (95% CI=72.7 to 86.8%) considering similar primary care systems.^{17,18} In symptomatic patients presenting to primary care, the sensitivity of chest radiograph to detect lung malignancy is 81%, with specificity 68% and this implies a high risk of false-negative.¹⁹ A key factor is nodule appearance. Lung lesions in apical, hilar, retrocardiac, and retro diaphragmatic locations as well as lesion size or density of nodules limit the detection rate in a routine posteroanterior chest radiography.²⁰ In the index case, the chest radiograph before surgery failed to pick up the lesion. Chest X-ray fails to identify LC (mostly initially) in more than 20% of people who are subsequently diagnosed with LC.¹⁹ No one should be reassured by a negative chest radiograph if there is a high clinical suspicion for malignancy, and cross-sectional imaging should be considered. Fortunately, low dose computed tomography (LDCT) has shown to be a potential tool for screening of LC in people at risk for exposure to tobacco smoke.²¹ AIOM 2020 guidelines' authors have produced a systematic review and meta-analysis whose goal is to summarize the available evidence on the efficacy of LC screening by combining randomized clinical trials comparing computed tomography screening (CTLS) versus NO screening (NS) or chest radiography (CXR) screening in smokers or former ones to estimate the benefits and risks associated with screening. The pooled analysis shows that CTLS screening is associated with a significant increase in the surgical resection rate and, therefore, a reduction in LC-related mortality of about 20%.²⁰ CTLS in this selected population allows obtaining a significant increase of early stage tumors diagnosis (stage IA).^{22,23} Finally, the U.S. Preventive Services Task Force (USPSTF) recommends annual screening for LC with LDCT in adults aged 50–80 years who have a history of 20 packs of cigarettes and currently smoke or have quit within the last 15 years. The same guidelines recommend stopping screening when a



FIGURE 6 TC Scan showing a large amount of lymph node tissue in the left perihilar posterior to the ipsilateral main bronchus.

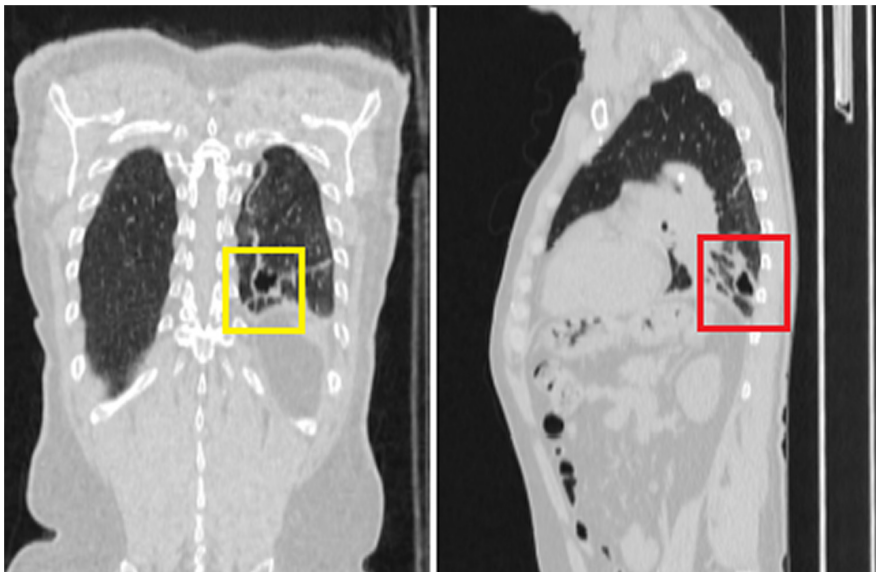


FIGURE 7 Cavitory lesion in left basal lung area of about 2.5 cm.

person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to undergo curative lung surgery.²⁴

More than ultrasound and/or computed tomography exam and PET, FNAB is a useful tool for differential diagnosis between metastasis to the thyroid gland and primary

thyroid cancer. However, lung adenocarcinoma and papillary thyroid carcinoma share architectural and nuclear changes and both lesions display TTF-1 expression.²⁵ Thyroglobulin differentiates primary thyroid tumor from lung one but, in case of poor differentiation, differentiating metastatic lesion in thyroid gland is not easy.²² In fact,



FIGURE 8 Chest X ray scan before starting any treatment.

FNAB accurately diagnosed metastatic disease in 58% of cases, while it identified a thyroid malignancy in approximately 90% of cases.²³

Fine-needle aspiration (FNA) cytology coupled with needle-wash thyroglobulin (FNA-Tg) testing is recommended for detection of cervical lymph node metastasis in patients with papillary thyroid carcinoma, but this test has some limitations. For example, patients with high FNA-Tg level have no positive lymph node specimens and this is likely due to contamination in case of intact thyroid. FNA-Tg testing cannot substitute conventional cytology due to high rate of false-negative thyroglobulin lab results as well as high rate of false-positive thyroglobulin testing due to blood contamination in patients with thyroid, thyroid cancer with loss of thyroglobulin expression, or as in our case lymph node metastasis from other origins.²⁶

4 | CONCLUSION

The important lesson to be learned from our case report is that the possibility of long-distance metastasis must be considered in the differential diagnosis of any cervical lymph nodes metastasis, especially when thyroid nodule subjected to FNAB results negative. This is particularly true when lymph node cytological evaluation does not provide useful guidance for management of the case or, as in this case, is inconsistent with thyroid cytological findings and sonographic features.²⁷ In such situations, metastasis can be the first sign of an unsuspected cancer, such as LC. Management decisions in these cases require multidisciplinary input and need additional diagnostic tools, like neck and chest CT scans, rather than immediate surgery. The risk involved is performing surgery on a patient who has not been thoroughly studied and most importantly, not carefully staged.

AUTHOR CONTRIBUTIONS

Chiara Scorziello: Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Maria Carola Borcea:** Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Marco Biffoni:** Investigation; methodology. **Angelina Pernazza:** Data curation; resources; writing – original draft. **Francesca Arienzo:** Data curation; resources; writing – original draft. **Rossella Melcarne:** Investigation. **Luca Ventrone:** Investigation. **Angelo Laca:** Investigation. **Giorgio Grani:** Investigation; methodology. **Cosimo Durante:** Investigation; methodology. **Fabrizio Consorti:** Methodology; supervision; validation. **Laura Giacomelli:** Methodology; supervision; validation.

CONFLICT OF INTEREST STATEMENT

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Informed written consent was obtained from the patient.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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