

Pulmonary Metastases- Imaging Spectrum from Different Primaries

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Abstract

Background: Lung is an extremely common site for metastasis. Different imaging patterns of lung metastases help not to miss the diagnosis of metastasis, so that by giving early treatment, morbidity and mortality can be reduced. The aim & objective is to illustrate the different imaging patterns of pulmonary metastases from different primaries. **Subjects and Methods:** This is a retrospective descriptive study. We have taken 30 cases of pulmonary metastasis with different primary malignancies and observed the atypical radiologic features of metastases from different primaries. **Results:** In our institute out of 30 cases of pulmonary metastases of which 4 (14%) cases of Renal cell carcinoma, 2(7%) cases of testicular germ cell tumor, 4 (13%) cases of thyroid cancer, 2(7%) cases of osteosarcoma, 4(13%) cases of GI tract adenocarcinoma, 3 (10%) cases of gynecological malignancies, 1(3%) case of femoral vein leiomyosarcoma, 4 (13%) cases of breast cancer, 1(3%) case of lymphoma, 5 (17%) cases of lung carcinoma showed different patterns of pulmonary metastases along with typical pattern, i.e., multiple soft tissue density nodules. Summary: The atypical radiologic features of metastases observed were cavitation, calcification, endobronchial metastases, ground-glass attenuation around mass (CT halo sign), and consolidation with or without ground-glass opacity. **Conclusion:** Multiple round variable-sized nodules and diffuse thickening of the interstitium are typical radiologic findings of pulmonary metastasis. Different patterns make it difficult the diagnosis of pulmonary metastases. So, the knowledge of different patterns of pulmonary metastases from different primaries helps in the early diagnosis of metastases.

Keywords: pulmonary metastasis, patterns, atypical radiologic features.

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Introduction

The lung is a very common site for metastases. Different imaging patterns of lung metastases help not to miss the diagnosis of metastases, so that by giving early treatment morbidity and mortality can be reduced.

Therefore immense knowledge of pathophysiology, radiological features of metastatic disease, and differential diagnosis is necessary for a radiologist.

Breast, lung, colorectal cancer, uterine leiomyosarcoma, and head/neck squamous cell carcinomas are the common cancers that metastasize to the lung parenchyma. Colorectal, renal, lung cancer, and lymphomas are the cancers that spread to the endobronchial tree of the lungs. Osteosarcoma, testicular tumors are the other tumors that can metastasize to the lungs. Adrenal, thyroid, choriocarcinoma, hypernephroma are the other rare cancers

that metastasize to the lung.^[1]

Etiology: Hematogenous, lymphatic route or by direct invasion are the various routes by which tumors spread to the lungs.

Hematogenous spread: seen in tumors with venous drainage into lungs, e.g., kidneys, osteosarcoma, testes, adrenals, melanoma, head and neck, and thyroid.

Lymphatic spread: occurred in two ways: either by retrograde lymphatic spread from hilar nodal metastases or antegrade lymphatic invasion through the diaphragm and/or pleural surfaces. Examples include lung, stomach, breast, pancreas, uterus, rectum, and prostate cancer.

Direct spread to pleura: Examples include cancers of the lung, breast, pancreas, and stomach.^[1]

This study aims to illustrate the different imaging patterns in Pulmonary metastases from different primaries.

This article is limited to a explanation of different pulmonary parenchymal metastases.

Typical imaging findings of a pulmonary metastasis comprise multiple peripherally located round variable-sized nodules (hematogenous metastasis) and diffuse thickening of the interstitium (lymphangitic carcinomatosis). 73% were reported to be pulmonary metastases among cases of multiple nodules detected with CT.^[2]

Hemorrhage around the metastatic nodules, cavitation, calcification, tumor embolism, endobronchial metastasis, solitary mass, dilated vessels within a mass, pneumothorax, air-space pattern, and sterilized metastasis are the atypical radiologic features of metastases which are frequently encountered in daily practice.

This makes the diagnosis difficult.^[2]

Imaging patterns of metastatic spread:

Malignancies of the head and neck, thyroid, adrenals, kidneys, testes, melanoma, and osteosarcoma are the tumors with venous drainage directly into the lung showing hematogenous spread.

Cavitation - (squamous cell carcinoma of the head and neck and from the genitourinary tract in women).

Diffuse miliary seeding - (papillary and medullary carcinoma of the thyroid).

Large singular metastases - (choriocarcinoma, melanoma, and hypernephroma).

Calcification - (osteosarcoma, adenocarcinoma, and secondary to chemo- and radiation therapy).

Aims & Objective

This study aims to illustrate the different imaging patterns in Pulmonary metastases from different primaries.

Subjects and Methods

The study design is descriptive. Case records of the hospital in the period January 2017 to December 2020 were searched using the keyword metastases to lungs in the

hospital information system. Retrospective evaluation from case records of all patients with a diagnosis of pulmonary metastases, which are radiologically and histologically proven. The clinical, imaging, and histopathological records of the total of 40 patients were evaluated.

Ten patients were excluded because available records were not optimal. Imaging of the remaining 30 patients that forms the study group was evaluated in detail. No informed consent was obtained from these patients as the study was retrospective.

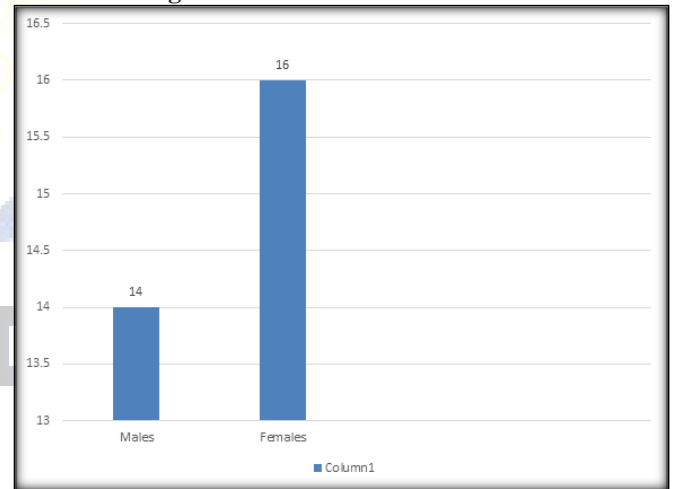
The scan was performed on GE OPTIMA 128 SERIAL SLICE CT scanner in all patients.

All the patients were scanned using a standard protocol. All images were seen on a workstation and get back from the picture archiving and communication system.

Results

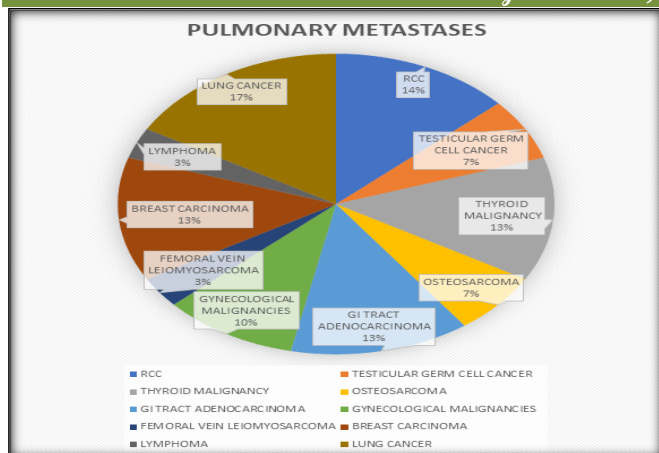
We studied 30 patients ranging between 21 to 82 years of age, with the majority of them presenting between 50 to 82 years of age.

The sex and age distributions:



Age in years	No. of patients	Percentage
<50	9	30
50-60	7	23.4
60-70	9	30
>70	5	16.6

No. of cases	Primary	Imaging pattern of pulmonary metastases
4	RCC	4 cases showed typical appearance like multiple soft tissue density nodules
2	Testicular germ cell tumor	2 cases showed large peripherally located soft tissue density nodules
4	Thyroid cancer 3- Medullary thyroid carcinoma 1-Papillary thyroid carcinoma	MTC showed multiple soft tissue density nodules. Papillary thyroid carcinoma showed a miliary pattern.
2	Osteosarcoma	2 cases showed multiple large nodules with extensive central calcification showing a sunburst pattern.
4	GI tract adenocarcinoma	3 cases showed a typical pattern. 1 case showed a consolidation pattern containing an air bronchogram.
3	Gynecological malignancy Endometrial cancer-2 Cervical cancer-1	Cervical cancer showed few cavitory lesions. Endometrial cancer showed multiple soft tissue density nodules.
1	Femoral vein leiomyosarcoma	multiple heterogeneously enhancing soft tissue density nodules in bilateral lung fields.
4	Breast carcinoma	1 case showed endobronchial localization, 3 cases showed multiple pulmonary nodules.
1	Lymphoma	Multiple soft tissue nodules interspersed with background fibro bronchiectatic lung disease with extensive abdominal and mediastinal lymphadenopathy.
5	Lung carcinoma	Multiple sub-centimetric soft tissue density nodules are scattered throughout the opposite lung parenchyma.



Representative cases:

CASE 1: Renal cell carcinoma with pulmonary metastases

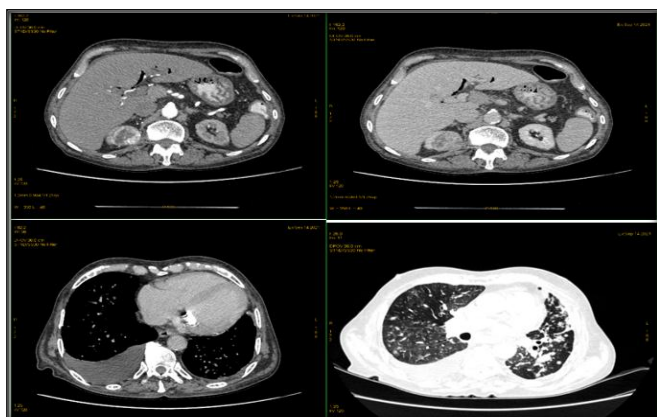


Figure 1: A well defined hypodense lesion in upper pole of right kidney showing heterogenous enhancement on arterial phase and wash out in the delayed phase. Multiple nodular densities of varying sizes and few centrilobular nodules in bilateral lungs.

CASE 2: Cystic RCC with metastases to lungs

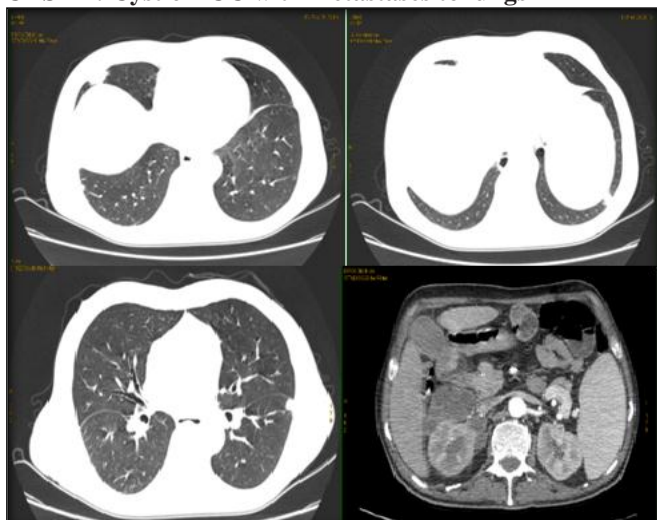


Figure 2: Ill-defined loculated peripherally enhancing subcapsular cystic lesion encircling renal hilar vessels. Few sub pleural nodules in bilateral lungs.

Case 3: Testicular germcell tumour with metastases to lungs

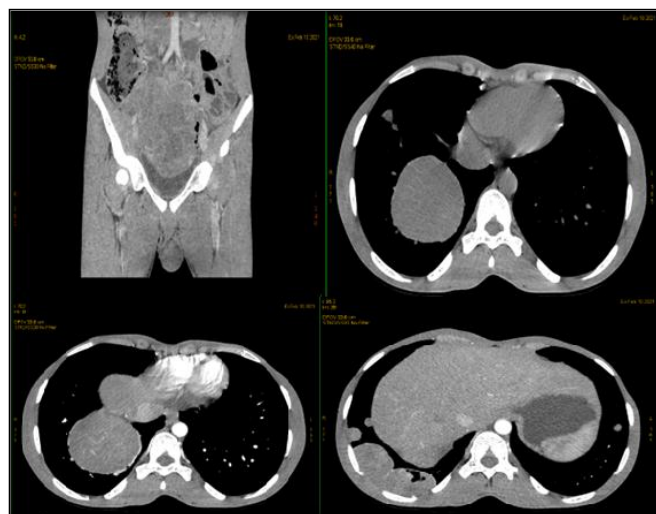


Figure 3: A large heterogeneously enhancing mass lesion in pelvis in a patient with right undescended testis. Note testis in left hemi scrotal sac. Large peripherally located soft tissue nodules showing mild contrast enhancement in bilateral lungs. HPE suggests testicular seminomatous germ cell tumor with lung metastases.

Case 4: Thyroid Malignancy Metastases to Lungs



Figure 4: Ill defined heterogeneously hypodense lesion with few calcific foci meas.4x3x4cm(APXTRXCC) in right lobe of thyroid causing tracheal shift to left side. Few subcentimetric soft tissue density nodules in bilateral lungs. On HPE it confirms medullary carcinoma of thyroid.

Case 5: Osteosarcoma metastases to lungs.

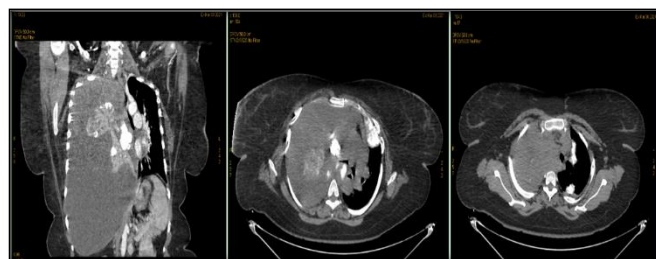


Figure 5: Known case of left hip disarticulation for aggressive recurrent high-grade osteosarcoma. Multiple large nodules with extensive central calcification showing sunburst pattern and enhancement on post contrast in collapsed right lung. Multiple large nodules with similar characteristics in left lung. Gross right pleural effusion.

Case 6: Pancreatic adenocarcinoma with metastases to lungs.

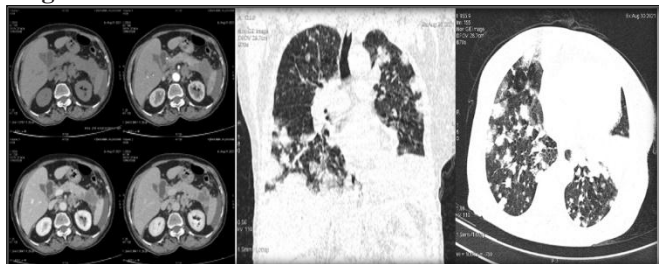


Figure 6: An ill-defined peripherally enhancing multilobulated hypodense lesion arising from tail of pancreas. Multiple patchy consolidation areas and nodular opacities in bilateral lungs. On HPE adenocarcinoma of pancreas was confirmed.

Case 7: Cervical cancer showing cavitary metastases

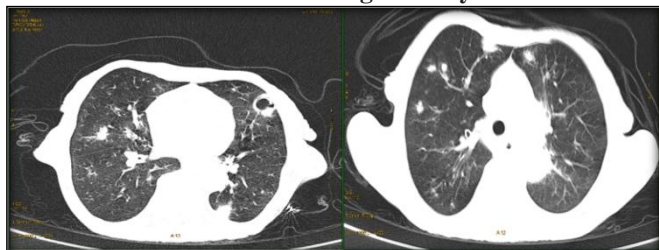


Figure 7: Multiple nodular opacities and cavitary changes noted in bilateral lungs with known case of cervical cancer.

Case 8: Soft tissue sarcoma with metastases to liver and lungs.

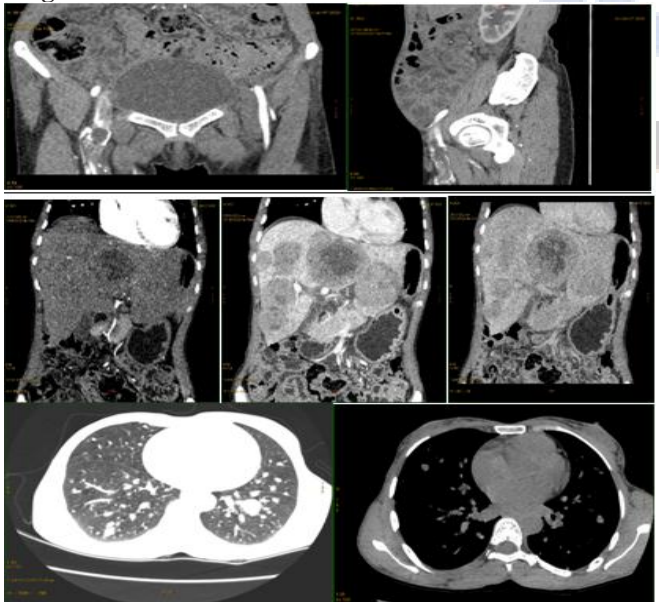


Figure 8: A large well defined heterogeneously peripherally enhancing lesion in right thigh arising from femoral vein causing expansion of the vein and replacing the vein. -Femoral vein leiomyosarcoma. Heterogenously enhancing linear filling defect extending from tumor site upto the external iliac vein on right side, suggesting tumor thrombus Multiple well defined heterogenous hypodense lesions in both lobes of liver showing peripheral heterogenous enhancement in arterial phase with few arterial feeders from hepatic artery and progressive enhancement in subsequent phases with internal non enhancing necrotic areas without any washout. Multiple soft tissue density nodules in bilateral lungs.

Case 9: Breast carcinoma metastases to lungs.

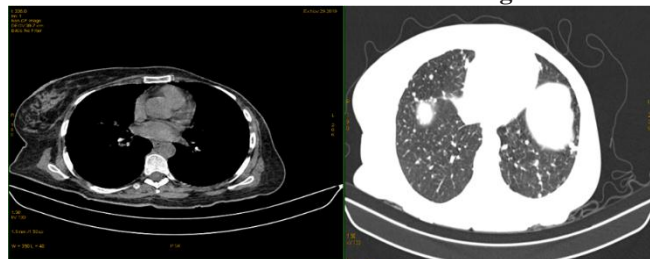


Figure 9: Known case of breast carcinoma undergone mastectomy of left breast. Diffusely scattered soft tissue density nodules in bilateral lungs.

Case 10: Carcinoma of lung with multiple metastases.

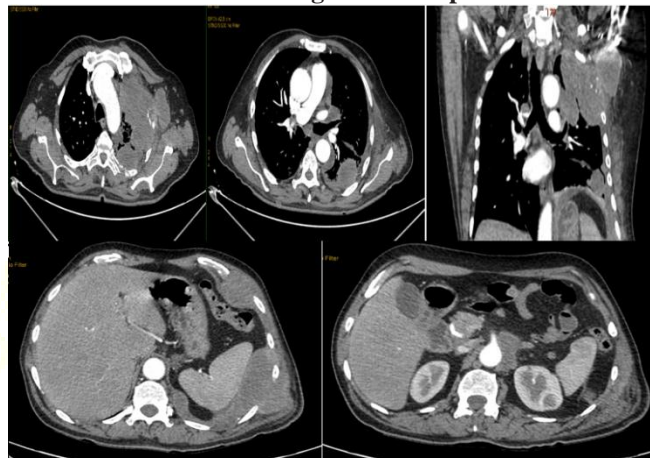


Figure 10: Multiple well defined conglomerate soft tissue density lesions in the left hemithorax, left lateral chest wall, left anterior and posterolateral abdominal walls, intra and retroperitoneal regions with respective rib destructions, mediastinal and mesenteric metastatic lymphadenopathy. Multiple subcentimetric soft tissue density nodules in right lung also.

Case 11: Lymphoreticular malignancy like lymphoma metastases to lungs

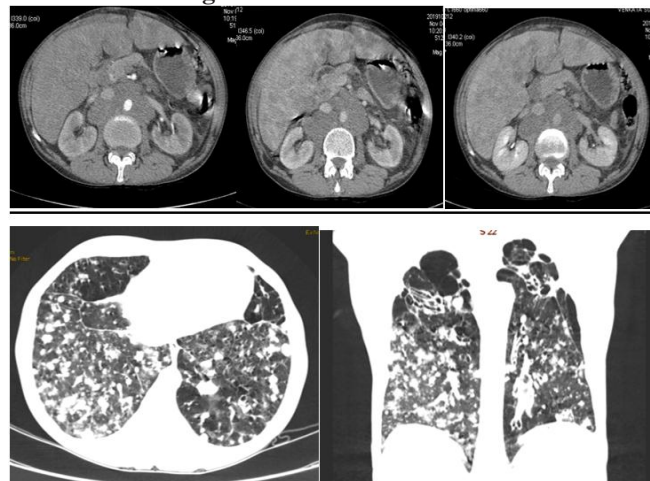


Figure 11: Multiple ill defined hypoenhancing lesions in both lobes of liver. Conglomerate hypoenhancing lymphnodes in prevertebral region extending from L2 to L5 encasing the aorta, IVC, bilateral renal arteries. Multiple soft tissue density nodules interspersed with background fibrobronchiectatic lung disease.

Discussion

Breast Carcinoma

According to Chikarmane et al., singular or multiple pulmonary nodules, endobronchial localization, air-space consolidation, and lymphangitic carcinomatosis, which may simulate other primaries such as pulmonary adenocarcinoma or lymphoma are the different patterns from breast cancer. Pleural localization is frequently revealed as a unilateral (and ipsilateral to the breast cancer) pleural effusion, with no specific features compared with benign effusions.^[12]

In our study out of 4 cases, 3 cases showed multiple pulmonary nodules and 1 case showed endobronchial localization.

Renal cell carcinoma:

According to Blanca Paño Brufau et al., almost 45% of metastases from RCC were pulmonary metastases. Pulmonary metastases are usually asymptomatic (90% of cases). Multiple nodules (75.6% of cases) or solitary nodules (30.5% of cases) are the findings on CT imaging. Well circumscribed, round or oval, smaller than 2 cm, subpleural located lesions are the usual findings. "cannonball" metastases do most commonly seen in RCC (ie, lesions > 5 cm in diameter). After antiangiogenic therapy lung metastases of RCC may show necrosis and cavitation. Necrosis and formation of bronchopleural fistulae in metastatic lesions after antiangiogenic therapy with that have wide contact with the pleura may show pneumothorax.^[4]

In our study Out of 4 cases, all cases showed Multiple soft tissue density nodules predominantly subpleural in location.

Gynecological Malignancies

According to Santiago Martínez-Jiménez et. al study,

1. Endometrial cancer (type 1 to type 3)

Multiple soft tissue density nodules and subpleural metastases.

2. Ovarian cancer -

From the transdiaphragmatic spread of peritoneal disease, Pleural metastases (nodules or effusions) are seen.

3. Cervical cancer- Cavitory lung metastases

4. Choriocarcinoma -

Hemorrhagic lung metastases ("halo" sign at CT)

5. Benign metastasizing leiomyomatosis:-

BML Asymptomatic patient with multiple solid lung nodules.

There will be a remote history of hysterectomy.^[5]

In our study out of 3 cases of gynecological malignancies, 2 were endometrial cancer and 1 was cervical cancer.

Pulmonary metastases from endometrial cancer showed multiple soft tissue density nodules.

Pulmonary metastases from cervical cancer showed few cavitory lesions.

Adenocarcinoma from GI tract

Adenocarcinoma metastases also spread into the lung in a lepidic fashion similar to bronchoalveolar carcinoma of the

lung. The imaging appearance can mimic pneumonia. According to Joon Beom Seo et.al, six of 65 patients with adenocarcinoma of the gastrointestinal tract had this pattern of metastasis. Focal or extensive ground-glass opacities, consolidation containing an air bronchogram, Air-space nodules, and nodules with CT halo signs are the radiologic findings of metastases from an adenocarcinoma.^[2]

In our study, out of 4 cases of metastases from GI tract adenocarcinoma, One case showed a consolidation pattern containing air bronchogram.

Thyroid malignancies:

According to Nina Ventura et al., Macronodular pattern, also known as a "cannonball" appearance, with clear-cut margins is commonly seen in Medullary carcinomas of the thyroid. Although the pulmonary micronodular patterns are seen more commonly in metastatic papillary thyroid cancer, they do also seen in Medullary thyroid cancer.^[19]

Granulomatous diseases, such as tuberculosis, histoplasmosis, or sarcoidosis usually show a micronodular pulmonary pattern, so can easily miss the diagnosis.

Reticulonodular perihilar lesions and calcified pulmonary metastases have also been reported in the literature. Very few cases have been reported to have micronodular patterns in medullary thyroid cancer in a review of the literature.^[19]

Due to Dystrophic calcification, an entity of mass with calcification occurs in papillary carcinoma of the thyroid.^[19]

In this study out of 4 cases, 3 cases were medullary thyroid carcinoma and 1 was papillary thyroid carcinoma.

3 cases of medullary thyroid carcinoma showed multiple soft tissue density nodules and 1 case of papillary thyroid carcinoma showed a miliary pattern of metastases.

Osteosarcoma

According to Seo et al., a Typical finding of benign lesions (granuloma or hamartoma) is usually calcification within a lung nodule, but calcification can also see in metastatic nodules from osteosarcoma or chondrosarcoma.^[2]

Osteogenic sarcoma, chondrosarcoma, synovial sarcoma, and giant cell tumor are the sarcomas reported in the literature to develop calcified lung metastases. Papillary and mucinous adenocarcinomas are the metastases most possibly develop calcified lung metastases. Many other tumors after antineoplastic therapy show calcification. Ossification of tumor cartilage, mucoid calcification, and dystrophic calcification are the different mechanisms of calcification seen in metastases from different primaries. Although calcification is a typical finding of benign lesions, reasonable suspicion for metastases is necessary for evaluating calcification in a pulmonary nodule.^[10]

In this study 2 cases are from osteosarcoma showed multiple large nodules with extensive central calcification showing sunburst pattern.

Testicular Cancer

According to Monica J. Wood et al. study, 15% of patients with NSGCT show pulmonary metastases at the time of presentation. Compared to seminomas Intrathoracic metastases occur 20 times more commonly in NSGCT. Larger nodules, measuring at least 1–2 cm and more homogeneous in attenuation are typically seen in metastases

from seminomas, whereas small peripheral bilateral pulmonary nodules frequently manifest in NSGCT.^[7] The most common cause for pulmonary metastases is hematogenous dissemination, lymphatic spread through the thoracic duct can also reach the left supraclavicular nodes and subsequently the lungs. Depending on histology, the pattern of mediastinal spread differs. NSGCTs spread in a less consistent pattern to the anterior mediastinum; aortopulmonary window; and hilar, supraclavicular, and cervical lymph nodes. NSGCTs do often sparing the posterior mediastinum and subcarinal regions, whereas Seminomas disseminate via the thoracic duct to the posterior mediastinum in a near-contiguous manner. 70% of metastatic testicular seminomas show mediastinal disease.^[7] In this study, 2 cases from seminomatous germ cell tumors of testis showed large peripherally located soft tissue density nodules.

Lymphoma

According to Bhoomi Angirish et.al, large masses, mass-like consolidation, nodules with or without cavitation, ground glass, and lymphangitis/ perilymphatic pattern are the patterns of lung involvement in lymphoma.^[8]

In this study, one case was diffuse lymphoma showed multiple soft tissue nodules interspersed with background fibrobronchiectatic lung disease with extensive abdominal and mediastinal lymphadenopathy.

Soft tissue Sarcoma

In this study, one case was pulmonary metastases from right femoral vein leiomyosarcoma showing multiple heterogeneously enhancing soft tissue density nodules in bilateral lung fields.

Lung Cancer

According to N C Purandare et. al, More than 50% of lung cancer patients present with metastatic disease. Common distant metastatic sites are Bones, adrenals, brain, and liver. M1a (intrathoracic metastasis) and M1b (Extrathoracic metastases) are the subclassifications under metastatic disease. M1a has a better prognosis than M1b. M1a disease includes malignant pleural effusion, pleural metastases, pericardial disease, and pulmonary nodules in the contralateral lung. M1b disease constitutes metastases to the bones, adrenals, liver, brain, and any other distant extra-thoracic site.^[15]

In this study 5 cases of pulmonary metastases from lung carcinoma as primary multiple subcentimetric soft tissue density nodules scattered throughout the bilateral lung parenchyma.

Conclusion

Multiple round variable-sized nodules and diffuse thickening of the interstitium are typical radiologic findings of pulmonary metastasis. Different patterns make it difficult the diagnosis of pulmonary metastases. So, the knowledge of different patterns of pulmonary metastases from different primaries helps in the early diagnosis of metastases and

their respective primaries.^[2]

References

1. Welch DR, Hurst DR. Defining the Hallmarks of Metastasis. *Cancer Res.* 2019;79(12):3011-3027. doi:10.1158/0008-5472.CAN-19-0458
2. Seo JB, Im JG, Goo JM, Chung MJ, Kim MY. Atypical pulmonary metastases: spectrum of radiologic findings. *Radiographics.* 2001;21(2):403-17. doi: 10.1148/radiographics.21.2.g01mr17403.
3. Hirakata K, Nakata H, Nakagawa T. CT of pulmonary metastases with pathological correlation. *Semin Ultrasound CT MR.* 1995;16(5):379-94. doi: 10.1016/0887-2171(95)90027-6.
4. Brufau BP, Cerqueda CS, Villalba LB, Izquierdo RS, González BM, Molina CN. Metastatic renal cell carcinoma: radiologic findings and assessment of response to targeted antiangiogenic therapy by using multidetector CT. *Radiographics.* 2013;33(6):1691-716. doi: 10.1148/rg.336125110.
5. Ventura N, Marchiori E, Zanetti G, et al. Medullary thyroid carcinoma with micronodular lung metastases: a case report with an emphasis on the imaging findings. *Case Rep Med.* 2010;2010:616580. doi:10.1155/2010/616580
6. Panicek DM, Toner GC, Heelan RT, Bosl GJ. Nonseminomatous germ cell tumors: enlarging masses despite chemotherapy. *Radiology.* 1990; 175:499-502.
7. Angirish B, Sanghavi P, Jankharia B. Pulmonary manifestations of lymphoma: A pictorial essay. *Lung India.* 2020;37(3):263-267. doi: 10.4103/lungindia.lungindia_200_19. P
8. Purandare NC, Rangarajan V. Imaging of lung cancer: Implications on staging and management. *Indian J Radiol Imaging.* 2015;25(2):109-120. doi:10.4103/0971-3026.155831.
9. Primack SL, Hartman TE, Lee KS, Muller NL. Pulmonary nodules and the CT halo sign. *Radiology.* 1985; 190:513-515.
10. Maile CW, Rodan BA, Godwin JD, Chen JTT, Ravin CE. Calcification in pulmonary metastases. *Br J Radiol.* 1982; 55:108-113.
11. Crow J, Slaviv G, Kreel L. Pulmonary metastases: a pathologic and radiologic study. *Cancer.* 1981; 47:2595-2602.
12. Chikarmane SA, Tirumani SH, Howard SA, Jagannathan JP, DiPiro PJ. Metastatic patterns of breast cancer subtypes: what radiologists should know in the era of personalized cancer medicine. *Clin Radiol.* 2015;70(1):1-10. doi: 10.1016/j.crad.2014.08.015.
13. Jimenez JM, Casey SO, Citron M, Khan A. Calcified pulmonary metastases from medullary carcinoma of the thyroid. *Comput Med Imaging Graph.* 1995; 19:325-328.
14. Maile CW, Rodan BA, Godwin JD, Chen JTT, Ravin CE. Calcification in pulmonary metastases. *Br J Radiol.* 1982; 55:108-113.
15. Martínez-Jiménez S, Rosado-de-Christenson ML, Walker CM, Kunin JR, Betancourt SL, Shoup BL, Pettavel PP. Imaging features of thoracic metastases from gynecologic neoplasms. *Radiographics.* 2014;34(6):1742-54. doi: 10.1148/rg.346140052.
16. Shepard JA, Moore EH, Templeton PA, McLoud TC. Pulmonary intravascular tumor emboli: dilated and beaded peripheral pulmonary arteries at CT. *Radiology.* 1993;187(3):797-801. doi: 10.1148/radiology.187.3.8497633.
17. Braman SS, Whitcomb ME. Endobronchial metastasis. *Arch Intern Med.* 1975; 135:543-547.
18. Steele JD. The solitary pulmonary nodule. *J Thorac*

Cardiovasc Surg. 1963; 46:21-39.

19. Wood MJ, Thomas R, Howard SA, Braschi-Amirfarzan M. Imaging of Metastatic Germ Cell Tumors in Male Patients From Initial Diagnosis to Treatment-Related Toxicities: A Primer for Radiologists. *AJR Am J Roentgenol.* 2020;214(1):24-33. doi: 10.2214/AJR.19.21623.
20. Toomes H, Delphendahl A, Manke H, Vogt-Moykopt I. The coin lesion of the lung: a review of 955 resected coin lesions. *Cancer.* 1983; 51:534-537.

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