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PET-CT - Inflammation or Cancer? Differentiation of Malignant or Benign Lung Nodules in PET/CT

Paleru C[1,2], Sandru AE[1], Nitipir C[4,2], Diaconu GA[1] and Munteanul[1,3]*

[1]"Marius Nasta" Institute of Pneumophtisyiology, Bucharest, Romania

[2]Carol Davila University, Bucharest, Romania

[3]Titu Maiorescu University, Bucharest, Romania

[4]Elias University Emergency Hospital, Bucharest, Romania

Abstract

Benign infectious or inflammatory processes can cause false-positive results in oncological PET-CT imaging, through the 18F-FDG metabolic activity they exhibit. The sequential PET/CT evaluation of post-infection COVID-19 in a patient with a pathological history of breast neoplasm has questioned the importance of PET/CT in tracking cancer versus scarring processes in COVID-19. It is not usual in medical practice to follow up a case with COVID-19 post-infection status by PET/CT examination, even less so by two PET/CT examinations performed at two months and three months post-infectious episode respectively, which is why the importance of publishing this article was decided.

Keywords: COVID-19; PET-CT; Cancer; Lung scarring

Introduction

18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) is routinely performed in cancer patients for staging of neoplasms and assessment of response to treatment. However, FDG uptake is not completely specific for cancer and, in addition to treatment-induced inflammatory changes, a variety of infectious and benign inflammatory processes can lead to focal FDG uptake. Positron Emission Tomography/Computed Tomography (PET/CT) used in the follow-up of a post-COVID-19 case at a short interval may pose the problem of differential diagnosis in the evaluation of the neoplastic patient [1,2].

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Correspondence:
Sandru Alexandra Emilia, "Marius Nasta" Institute of Pneumophtisyiology, Bucharest, Romania

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Materials and Methods

This article is a clinical case report and literature review. We included a 66-year-old patient with known treated neoplastic disease who was a victim of SARS-CoV-2 infection. Ethics committee approval was obtained, and the patient signed consent for his description in this paper. The literature review was performed using PubMed database, using keywords such as "PET-CT, lung nodule, malignant node, COVID-19".

Results

Patient aged 66 years, vaccinated against SARS-CoV-2, former smoker, weaned 15 years ago, with exposure to toxic chemicals for 30 years (laboratory worker).

She is known to have invasive ductal carcinoma G2 in the right breast radically removed in 2007 by right mastectomy and axillary lymphadenectomy, chemoradiotherapy and hormone therapy, without recurrence. From the history of the disease, we note that in April 2022, the patient is diagnosed with SARS-CoV-2 infection, and considering the personal pathological history and the potential for worsening of the disease, it is decided to administer monoclonal antibodies in a single dose, with good tolerance and favorable evolution. It is important to mention that the patient has undergone regular imaging evaluations since the time of diagnosis with breast cancer, including PET/CT (2009), with no lung nodular images (Figure 1).

In June 2022, the patient undergoes a PET/CT scan, for breast cancer follow-up, which does not find images of tumor recurrence in the left mammary gland, but depicts solid pulmonary nodular images, minimally metabolically active, SUV Lean Body Mass maximum 1.92, located in the dorsal segment of the left upper lobe and right lower apical, diameter 9 mm (Figure 2, 3) and metabolically active adenopathy, located left upper pre-vascular (Figure 4), (SUV LBM 9.80 and maximum

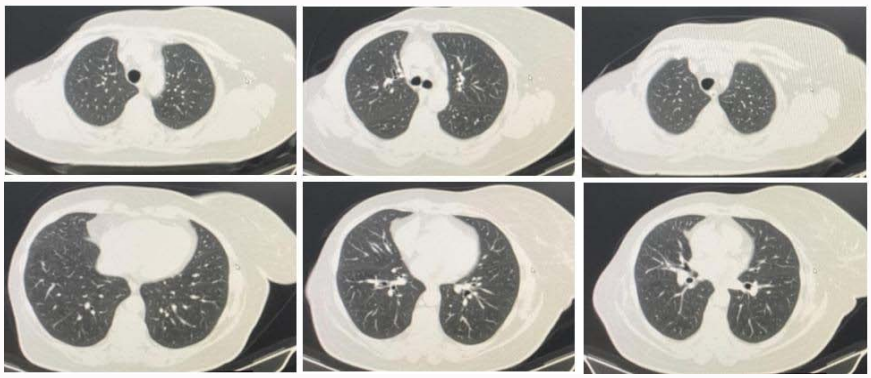

Figure 1: With no lung nodular images.

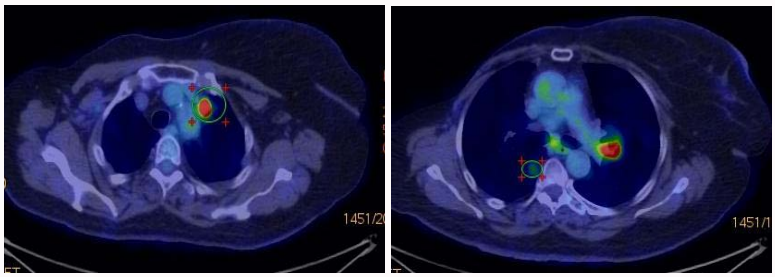

Figure 2, 3: The dorsal segment of the left upper lobe and right lower apical, diameter 9 mm.

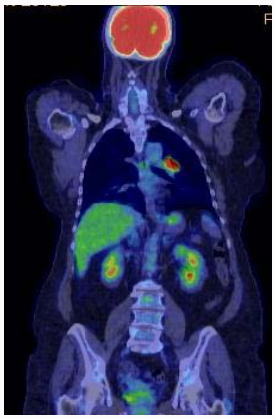

Figure 4: Metabolically active adenopathy, located left upper prevascular.

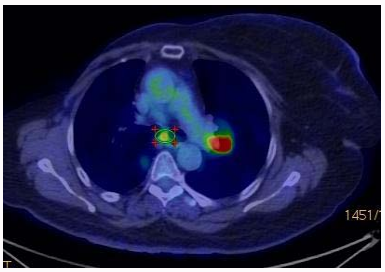

Figure 5: Infracarinal (SUV LBM 9.80 and maximum diameter 12 mm).

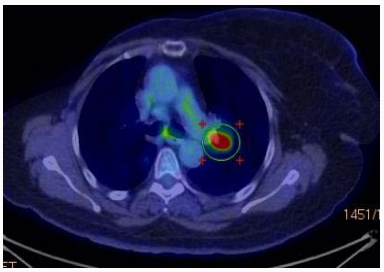

Figure 6: Left pulmonary hilum (SUV LBM 8.29 and maximum diameter 20 mm).

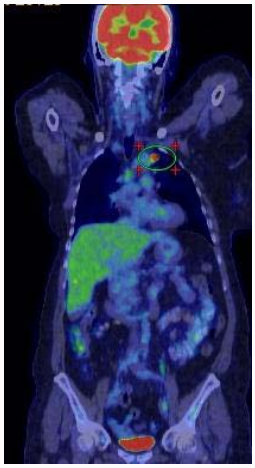

Figure 7: Metabolically active adenopathy.

diameter 12 mm), infracarinal (Figure 5) and left pulmonary hilum (SUV LBM 8.29 and maximum diameter 20 mm) (Figure 6, 7).

A bronchoscopy with biopsy/EBUS or mediastinoscopy is recommended at the oncological consultation, considering the high suspicion of bronchopulmonary neoplasm with secondary lymphangioma findings.

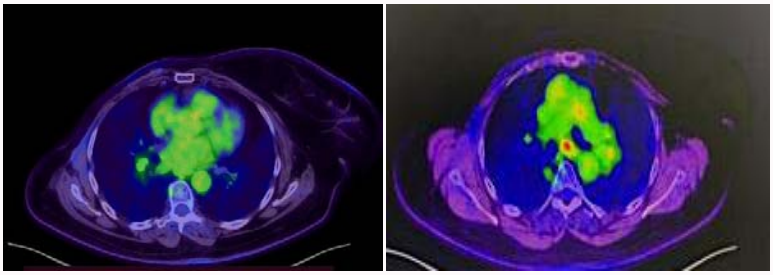

Figure 8, 9: Two pulmonary nodules with minimal metabolic activity.

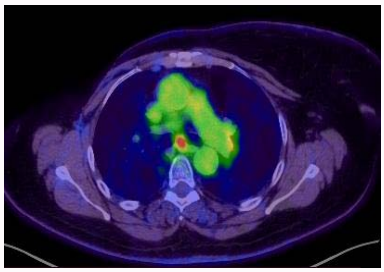

Figure 10: Infracarinal (metabolically active, SUV max 6.74, with dim 12/18 mm).

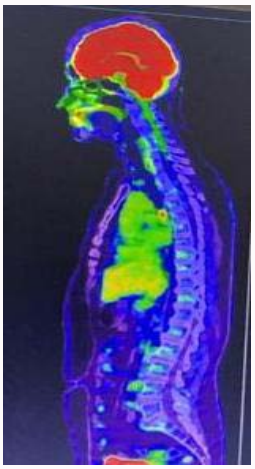

Figure 11: Inferior paratracheal (SUV max 3.03, dim 26/12 mm).

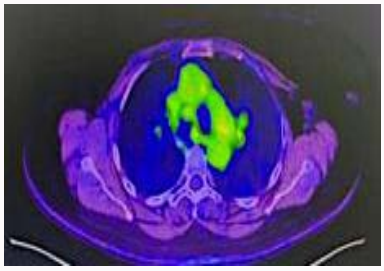

Figure 12: Inflammatory substrate of the present nodules.

In July 2022, the patient requests, without medical indication, another PET/CT scan, which further describes the two pulmonary nodules with minimal metabolic activity (Figure 8, 9), located at the apical segment - Right Inferior Lobe (SUVmax 2.31, axial diameter max 10 mm) and superior lingular segment (SUVmax 2.05, axial diam max 9 mm) and mediastinal adenopathy (Figure 10, 11) located

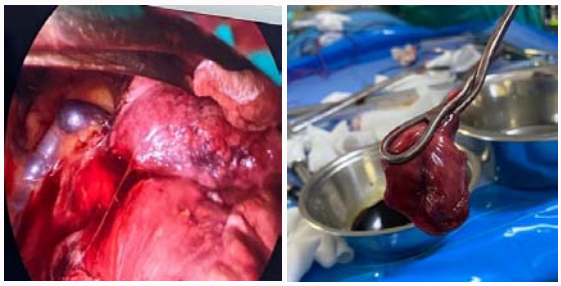

Figure 13, 14: Atypical right inferior lobe nodule resection and lymphadenectomy of right IV and VII nodes by right thoracoscopy.

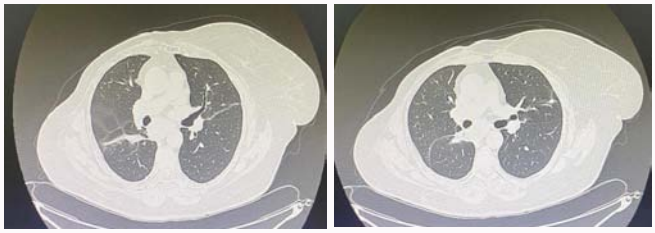

Figure 15, 16: Reassessment of native chest CT imaging with contrast medium at 3 months post-surgery.

infracarinal (metabolically active, SUVmax 6.74, with dim 12/18 mm) and inferior paratracheal (SUVmax 3.03, dim 26/12 mm), but with complete disappearance of left lesions (Figure 12), which points to an inflammatory substrate of the present nodules.

For a certain diagnosis of pulmonary nodules, in cooperation with the oncologist, it is decided in favor of surgery with atypical right inferior lobe nodule resection and lymphadenectomy of right IV and VII nodes by right thoracoscopy, with good postoperative evolution, without complications (Figure 13, 14).

Histopathological examination resulted as Right Lower Lobe pulmonary carcinomatous metastasis and station VII lymph node, most likely of infiltrative ductal carcinoma with mammary starting point, and station IV lymph node is described with numerous isolated and confluent minimally necrotizing granulomatous, epithelioid and giganto-epithelioid nodules (minimally necrotizing granulomatous lymphadenitis). Immunohistochemical examination of lung parenchymal fragment from RLL is performed, which supports the final diagnosis of lung metastasis of ER positive, PGR positive and HER2neu negative breast carcinoma.

The patient initiates treatment with IBRANCE protocol (Palbociclib-inhibitor CDK4/6) and Fulvestrant (estrogen blocker), with favorable response.

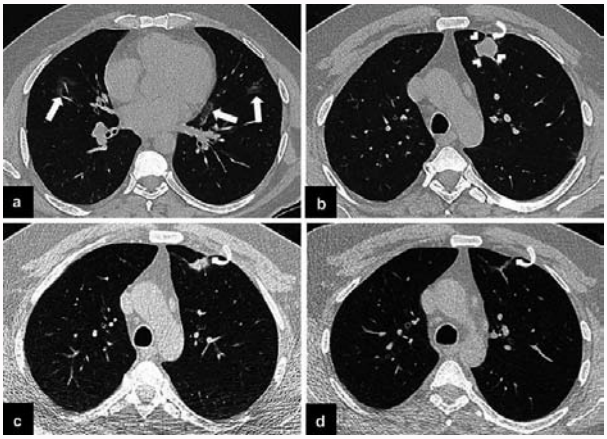

Figure 17: One of the many faces of COVID-19 infection: An irregularly shaped pulmonary nodule.

Reassessment of native chest CT imaging with contrast medium at 3 months post-surgery describes nodular formations located in the left lung area with reduced size compared to previous examinations and post-lung resection status with visible fibrosis lines in the right lower lobe (Figure 15, 16).

Discussion

The main clinical challenge remains to clearly differentiate infectious and inflammatory FDG uptake from malignancy. Currently, there is no such quantifiable measurement to guide towards a diagnosis. Unfortunately, although it is an easy parameter to obtain, no absolutely reliable Standard Uptake Value (SUV) threshold has been found that can be used to clinically differentiate benign from malignant uptake due to the similar mechanism of FDG accumulation between tumor cells and white blood cells [2].

Unexpected and incidental uptake foci in oncology PET/CT are relatively common. Given the increased uptake of 18F-FDG, infectious and inflammatory responses have the potential to be misinterpreted as metastatic disease. Following analysis of more than 1,000 patients undergoing 18F-FDG PET/CT, it has been reported in the literature [2] that more than a quarter of these scans contained foci of FDG uptake of benign origin attributed to infectious and non-infectious inflammation. Respiratory tract infections and brain infections were among the most common etiologies incidentally identified by PET/CT performed for oncological indications. The body responds to inflammatory stimuli with a cascade of events, including local hyperemia, release of proteins such as fibrin and immunoglobulins, and infiltration of inflammatory cells. Inflammation exhibits 18F-FDG uptake due to the recruitment of activated white blood cells (neutrophils and lymphocytes), which have a high affinity for glucose transporters, particularly GLUT 1 and GLUT 3.

COVID-19 infection can lead to various imaging findings, as it is the great radiological mimic, as reported by Duzgun et al. [1]. It is well known that the most common imaging finding of COVID-19 pneumonia is bilateral matted glass opacities accompanied by consolidation with thickening of interlobular or intralobular septa (crazy pavement pattern). Atypical findings are isolated lobar or segmental consolidation, interlobular septal thickening accompanied by pleural effusion, cavitations and solitary pulmonary nodules. Nodules represent one of the many facets of COVID-19 infection, with an incidence on CT scans of 3% to 12% in the literature [2]. Spontaneous regression of the solitary pulmonary nodule may be associated with the organization of pneumonia that has been shown to occur secondary to COVID-19 infection. Recognition of rare imaging cases of COVID-19 infection is essential for proper diagnostic and treatment management [3].

Similar cases with complete resolution of lung nodules have been reported in the literature and are associated with SARS-CoV-2 infection. One of these cases is of a 57-year-old patient, smoker, diagnosed with COVID-19 infection, imaging evaluation by computed tomography, with the detection of a 20 mm lung nodule, irregular in the left upper lobe (a, b). To rule out a possible primary lung cancer, given the history of chronic smoking, transthoracic percutaneous needle biopsy is planned. Pre-procedural chest CT shows regression of nodule size (c), so biopsy is postponed and re-evaluation is recommended at three months, when complete resolution of the left lung nodule is described (d) [1] (Figure 17).

It is unclear whether the pulmonary involvement of COVID-19 in cancer patients is different from that in the general population. Therefore, the development of new pulmonary nodules in a patient with a history of malignancy requires further evaluation [4].

The occurrence of metastases with a mammary starting point at a distance of 15 years is a rare phenomenon described in the literature. Most breast cancers metastasize about two years after the start of treatment, with another peak at 8 to 9 years. In a meta-analysis described by Dr. Rikke Norgaard, Dr. Buket Ozturk Esen and Dr. Lene Mellemkjaer, in a paper published in November 2021, following 36,924 women with breast cancer, 2,595 cases developed late metastases, 10 to 32 years after diagnosis. Women at risk for late recurrence are those with high lymph node burden, large tumor size, and estrogen receptor positivity, requiring more extensive surveillance or more aggressive treatment [5].

Approximately 75% of primary breast tumors have already spread by the time of diagnosis, seeding micrometastases at a regional or distant anatomical site. These micrometastases survive in a resting tumor state, whereby cell growth is balanced by apoptosis. Changes in cytokines, immune cells and growth factors in the tumor microenvironment leads to cessation of tumor rest, resulting in complete metastatic growth [5].

In breast cancer, understanding the mechanisms underlying cancer cell stagnation and retreatment is of crucial importance due to a particularly wide window of tumor recurrence, spanning up to two decades after diagnosis. Hypoxia, which occurs in patients with COVID-19 in the setting of respiratory distress and thrombosis, is a hallmark of micro-medial, poor prognosis of solid tumors. In breast cancer, hypoxia has been shown to be responsible for dormant cell generation by promoting expression of genes involved in cancer quiescence, drug resistance, stemness and EMT [6].

Throughout the pandemic, questions have been raised about how the SARS-CoV-2 infection, including its long-term effects, acts on cancer patients. Thus, it has been hypothesized that severe COVID-19 infection may increase the risk of subsequent cancer recurrence by inducing reactivation Of Latent Cancer Cells (LCCs). In a severe form of SARS-CoV-2, pathophysiological events such as immune-mediated tissue inflammation, impaired T-cell and Natural Killer (NK) cell activity, neutrophil hyperactivation and thrombocytosis occur, which may collectively generate a temporary pro-tumorigenic microenvironment favorable to LCC reactivation. Since the beginning

of the pandemic, ACE2 has been identified as the entry receptor for SARS-CoV-2. Although ACE2 has been reported to exert multiple antitumor effects, including inhibition of cancer angiogenesis and metastasis, its downregulation may itself promote tumor progression. Up-regulation of ACE2 causes hyperactivation of NF-kB, the most important molecule linking inflammation to cancer. NF-kB activation in cancer cells promotes proliferation, chemoresistance and invasion, while in the Tumor Microenvironment (TME) it stimulates angiogenesis and immune suppression, supporting the metastatic process [7].

Patients with the severe form of COVID-19 usually develop acute respiratory distress and Cytokine Release Syndrome (CRS), which can lead to sustained fever, edema, neurological symptoms, organ failure and shock. IL-6 plays a central role in the pathophysiology of CRS, and its high levels have been correlated with increased risk of tumor recurrence in breast cancer and head and neck cancer [7].

Recent studies have reported that NETs (Neutrophil Extracellular Traps), activate metastasis formation by several mechanisms, including the trapping of circulating tumor cells, activation of pro-metastatic fibroblasts and proteolytic destruction of the anti-tumorigenic factor thrombospondin-1. Importantly, NETs (Neutrophil Extracellular Traps), have been reported to awaken dormant breast cancer cells disseminated to the lungs [7].

The association between COVID-19 and increased risk of lung metastasis in patients with prior breast cancer should lead to specific follow-up programs and personalized therapies using anti-inflammatory agents capable of interfering with immune-mediated inflammatory pathways or NETs formation in order to decrease the risk of tumor recurrence [6].

Conclusions

PET/CT is a very useful tool in cancer diagnosis and follow-up, due to the high sensitivity of this imaging modality. Its specificity, however, may be reduced by the presence of infectious and inflammatory traps, the COVID-19 pandemic bringing new difficulties in tumor *vs.* inflammatory interpretation.

It is important to always be alert to these false-positive results, as they can influence the diagnosis and course of patient treatment. Patient pathological history is a mandatory step in navigating PET/CT imaging.

Before scheduling patients for 18F-FDG PET/CT scans for various oncological purposes, we must consider sources of possible interferences, such as COVID-19 infection, considering that there is no concise protocol indicating the time required for lesion resorption. Double PET/CT examination at a two-month interval shows the fleeting nature of the inflammatory capturing lesions three months after the COVID-19 infectious episode.

This case presentation is intended to increase awareness of the complications that COVID-19 disease can bring. In addition to many others, the effects of the pandemic can be felt indirectly, hindering the correct diagnosis of patients and decreasing the chances of survival. More similar case reports and other descriptive articles are needed to quantify the impact the pandemic has had on this type of situation.

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