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CASE REPORT

DUAL-TIME-POINT 18F-FDG PET/CT UNVEILED OCCULT HEPATIC METASTASIS OF BREAST CANCER

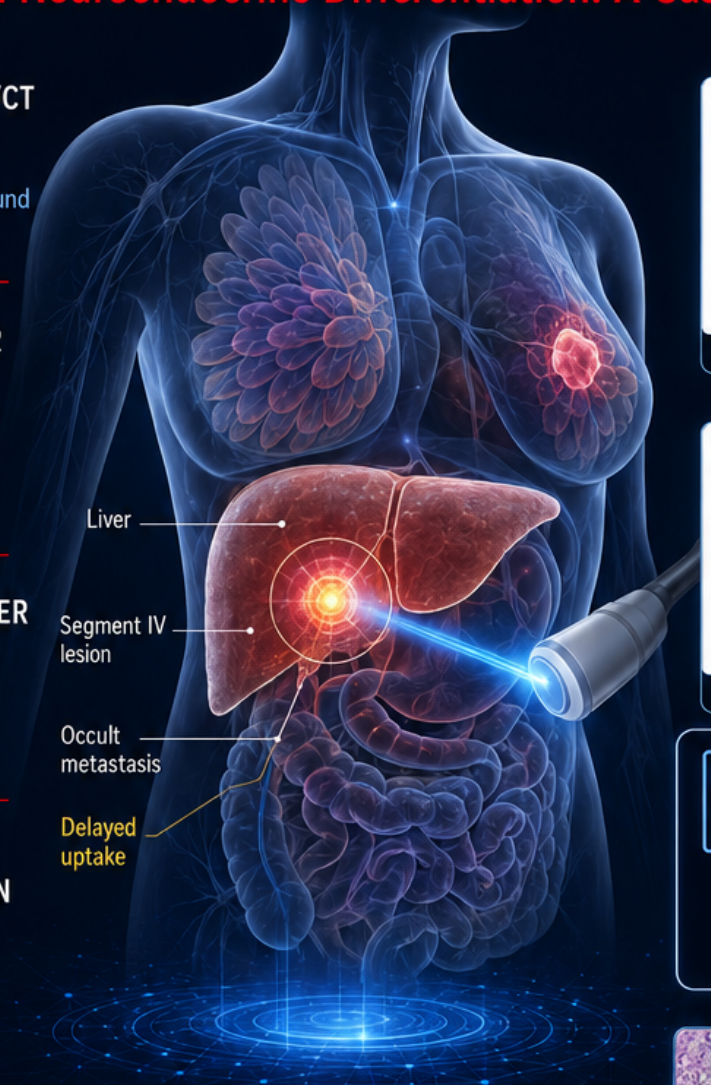
with Neuroendocrine Differentiation: A Case Report

DELAYED PET/CT
Dual-time-point imaging improves lesion-to-background contrast

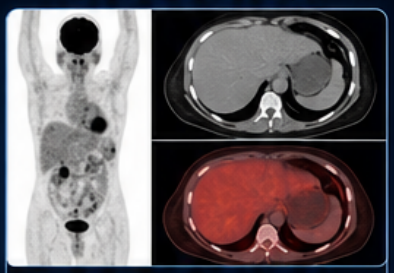
OCCULT LIVER LESION
Standard imaging negative; delayed imaging reveals focal uptake

BREAST CANCER RECURRENCE
Biochemical recurrence with rising CEA

PATHOLOGY CONFIRMATION
LCNEC of breast origin with neuroendocrine differentiation

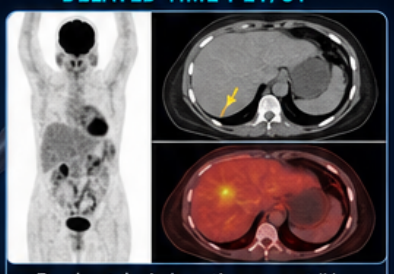


STANDARD-TIME PET/CT



No definite focal uptake in the liver

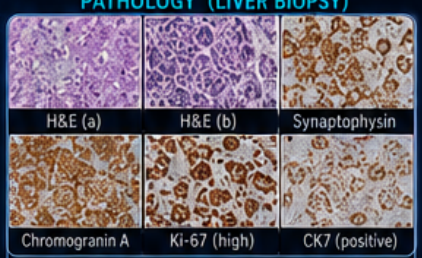
DELAYED-TIME PET/CT



Focal uptake in hepatic segment IV

THIS ISSUE
Case report on dual-time-point 18F-FDG PET/CT detection of occult hepatic metastasis from breast cancer with neuroendocrine differentiation.

PATHOLOGY (LIVER BIOPSY)



Neuroendocrine differentiation (LCNEC)

ONCOLOGIC IMAGING | DUAL-TIME-POINT PET/CT | BREAST CANCER METASTASIS | PRECISION MEDICINE

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Dual-time-point 18F-FDG PET/CT Imaging Unveiled Occult Hepatic Metastasis of Breast Cancer with Neuroendocrine Differentiation: A Case Report

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Abstract

Breast cancer with neuroendocrine differentiation is a rare entity, often presenting diagnostic challenges due to its atypical imaging features. Standard imaging modalities may fail to detect early metastases, particularly when tumour markers rise in isolation. A 57-year-old woman with a history of right-sided invasive ductal carcinoma (estrogen receptor (ER) positive, progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative) presented seven years after initial management with rising serum carcinoembryonic antigen (CEA) levels. Conventional imaging, including contrast-enhanced CT of the chest, abdomen and pelvis and standard-time 18F-FDG PET/CT, was negative. However, delayed PET/CT imaging (at 120 minutes) revealed a solitary metabolically active hepatic lesion with maximum standardized uptake value (SUVmax) 7.6, prompting further evaluation. Core biopsy identified the lesion as large cell neuroendocrine carcinoma (LCNEC) of breast origin, WHO grade 3. This case underscores the diagnostic value of delayed-phase 18F-FDG PET/CT in uncovering metabolically active occult liver metastasis from breast cancer in patients with biochemical recurrence and negative diagnostic imaging including routine 18F-FDG PET/CT. Delayed imaging in dual time point 18F-FDG PET/CT detected a focal hepatic lesion, guided biopsy and definitive characterization of its neuroendocrine differentiation, and enabled appropriately tailored management in keeping with precision medicine.

Keywords: Delayed PET/CT, breast cancer, neuroendocrine differentiation, liver metastasis, tumor markers, diagnostic imaging, occult metastasis.

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Background

Tumour markers are commonly used in practice in the surveillance of breast cancer patients. However, elevated markers such as carcinoembryonic antigen (CEA) in the absence of elevated primarily breast-cancer-associated tumour markers (i.e. Ca-15-3) and clear radiological evidence of recurrence often pose a diagnostic challenge.

Breast cancer is among the most prevalent malignancies in women worldwide. While metastatic spread is well-documented, transformation or progression to neuroendocrine-differentiated subtypes is exceptionally rare and may present diagnostic difficulties.

Traditional imaging modalities may miss early or atypical metastatic lesions, especially when serum markers such as CEA rise in isolation. In this context, dual-time-point 18F-FDG PET/CT imaging, acquiring delayed images, can play a pivotal role in uncovering metabolically active disease that evades standard detection.

Case Presentation

A 57-year-old female with a history of right-sided grade III invasive ductal carcinoma (ER positive, PR positive, HER2 negative, Ki67 35%) underwent right modified radical mastectomy in July 2017, followed by radiotherapy and two years of hormonal therapy. IHC stains for neuroendocrine differentiation were not performed, as they are not requested routinely.

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In November 2024, serum tumour markers, particularly CEA, slightly rose to 5.49 ng/mL from 3.82 ng/mL in August. Standard 18F-FDG PET/CT was negative. By March 2025, CEA reached 9.25 ng/mL raising concern despite a normal bilateral sonomammography and multiphase contrast-enhanced CT [Figure 1]. This period of diagnostic uncertainty, stretching over several months with conflicting biochemical and imaging results, was a source of significant anxiety for the patient, who remained otherwise asymptomatic.

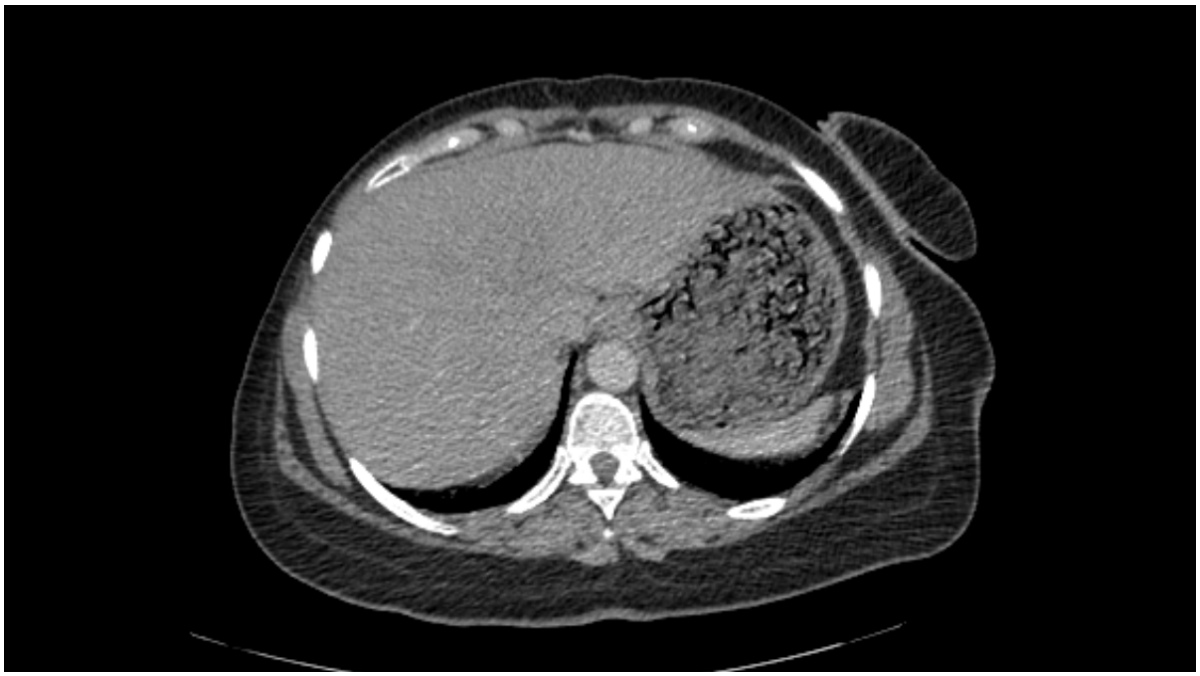

Fig. 1. Axial contrast-enhanced CT image of the abdomen showing no definitive hepatic lesion.

A second standard PET/CT (45 minutes post-injection) showed no uptake [Figure 2], but delayed imaging (120 minutes) revealed a solitary hepatic lesion in segment IV (SUVmax 7.6) [Figure 3]. It was not confidently visualized on prior multiphasic contrast-enhanced CT, likely due to its peri-portal location and minimal density gradient relative to the adjacent parenchyma, making it radiologically inconspicuous. The left breast operative bed, both lung fields, and rest of the body revealed no suspicious masses or hypermetabolic lesions.

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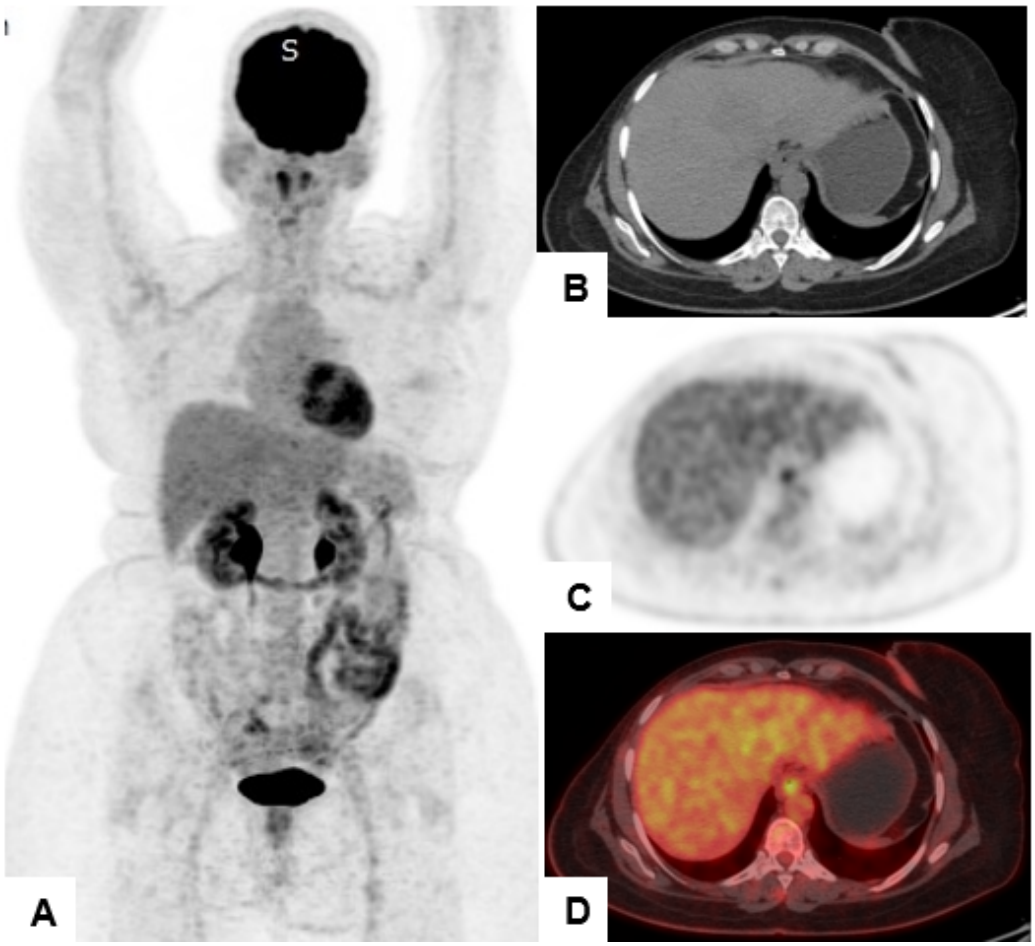

Fig. 2. Standard-time-point 18F-FDG PET/CT images showing no definitive hepatic lesion. (A) Maximum-intensity-projection FDG-PET image; (B) axial CT image; (C) corresponding axial PET image; and (D) fused PET/CT image acquired 45 minutes after injection. Physiological hepatic uptake is present.

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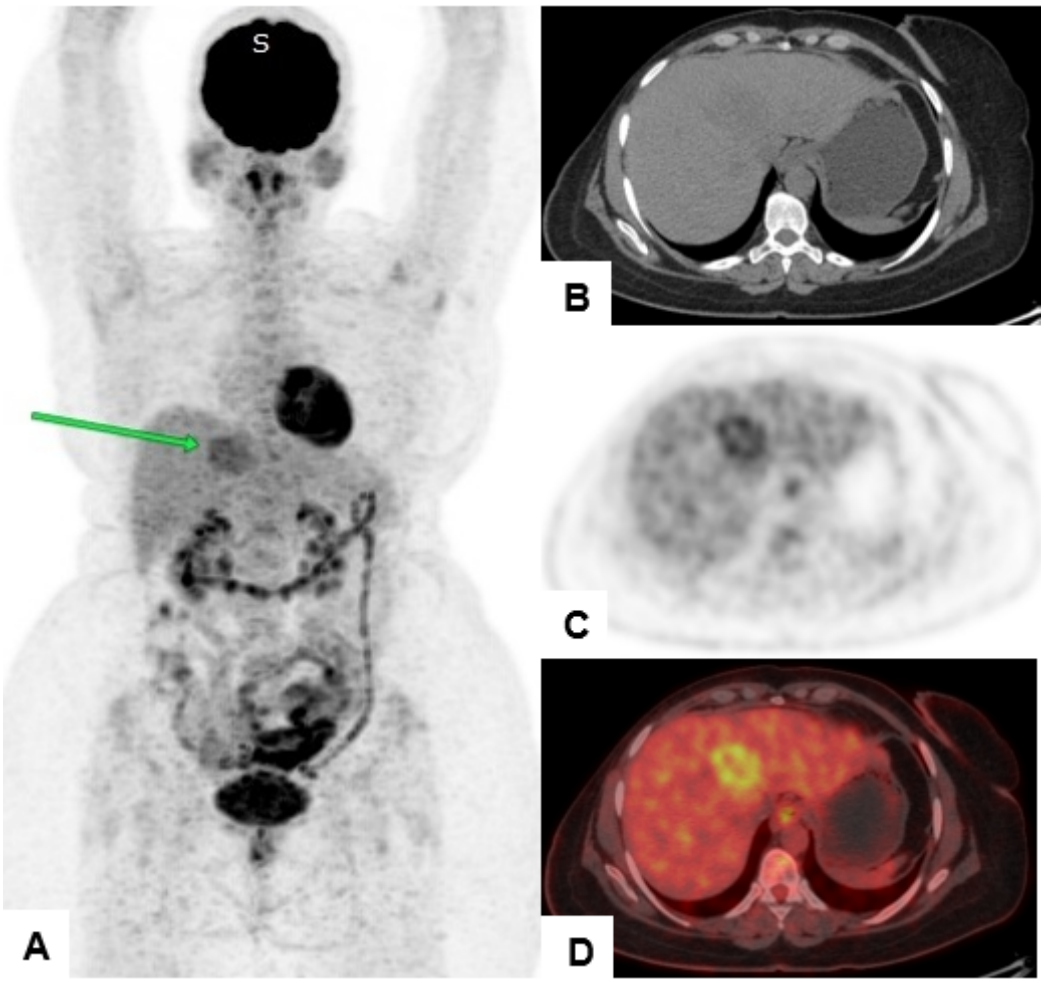

Fig. 3. Delayed 18F-FDG PET/CT images highlighting a hypermetabolic lesion in segment IV of the liver. (A) Maximum-intensity-projection FDG-PET image; (B) axial CT image; (C) corresponding axial PET image; and (D) fused PET/CT image acquired 120 minutes after injection. The solitary lesion demonstrates an SUVmax of 7.6, with reduced hepatic background activity.

Based on the 18F-FDG PET/CT images we provided to the interventional radiology team, a successful ultrasound-guided liver biopsy was performed and histopathologic examination revealed a high-grade neuroendocrine neoplasm (NEN); CK7: Positive, CK20: Negative, Chromogranin: Positive, Mammaglobin: Negative, Ki67: 20% [Figure 4].

The findings so far suggested a neuroendocrine tumour (WHO grade 3), either of an unknown primary source or a primary liver origin, a situation much less likely according to literature [1]. To add to this diagnostic dilemma, clinical suspicion remained that it could be a metastasis from the prior breast cancer, partly due to undetected primary location of NET in the surveyed body, specifically the pancreas, lungs and GIT. Furthermore, no hormonal syndromes (functional symptoms) were noted and the patient was asymptomatic, prompting more suspicion in the pathological diagnosis.

Further histopathological and immunohistochemical analysis were requested. A review of pathology slides for a second opinion also suggested a neuroendocrine tumour. Additional immunohistochemical analysis revealed strongly positive GATA3 [Figure 4d], a relatively high sensitivity and specificity marker for urothelial and breast carcinoma, including expression in all histological subtypes of breast carcinoma [2]. Furthermore, the hepatic focal lesion proved to be

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ER strongly positive, PR strongly positive, Ki67 20%, and, in contrast to the primary breast tumour, HER2 positive with mild membranous staining of more than 30% of tumour cells [Figure 4].

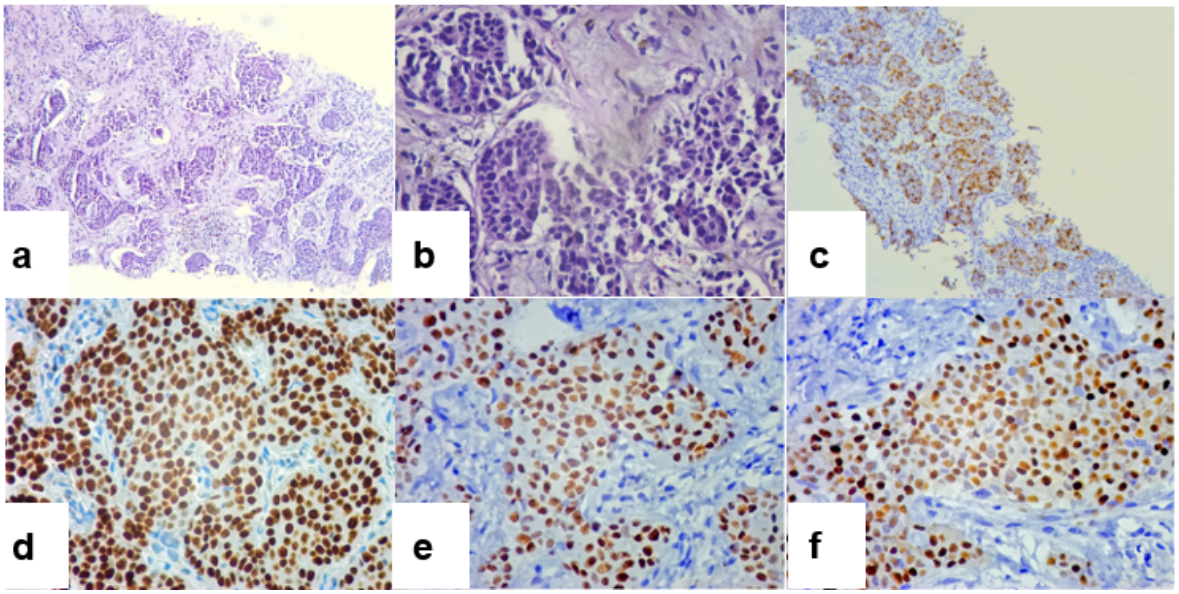

Fig. 4. Histopathology and immunohistochemistry of the liver-lesion biopsy. (a, b) Hematoxylin and eosin staining shows a poorly differentiated carcinoma with neuroendocrine features, including nesting and granular chromatin (original magnification ×100 and ×400). (c) Chromogranin A positivity in tumour cells (×100). (d) Strong nuclear GATA3 positivity in tumour cells (×400). (e, f) Positive ER and PR staining in tumour cells.

These findings were consistent with large cell neuroendocrine carcinoma (LCNEC) of breast origin, WHO grade 3, based on immunophenotyping and clinical context. Management was adjusted accordingly. The patient was referred for systemic therapy, after which the need for local therapy to the liver lesion would be determined. The medical oncology team decided to start with the weekly paclitaxel 80 mg/m² and 3-weekly carboplatin AUC 5 doublet.

Discussion

Delayed 18F-FDG PET/CT Imaging in Breast Cancer

This case illustrates the added diagnostic value of delayed-time-point 18F-FDG PET/CT imaging. In hepatic lesions, especially those surrounded by physiologic background uptake, early imaging can be inconclusive. Delayed imaging improves lesion-to-background contrast, enhancing the detection of metabolically active lesions that may otherwise be obscured in early images [3].

Studies have found that delayed imaging can improve lesion detection, especially in the liver, by increasing the contrast between lesions and normal tissue thus enhancing lesion to background ratio [3–5].

Of note, the lesion in our patient demonstrated FDG avidity, which aligned with the high-grade and poorly differentiated nature of the neuroendocrine tumour. This is consistent with established evidence showing that 18F-FDG PET/CT is more sensitive for high-grade (G3) and poorly differentiated NETs, whereas well-differentiated (G1–G2) NETs often have low or absent FDG uptake [6,7]. In contrast, 68Ga-DOTATATE PET/CT has emerged as the imaging modality

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of choice for well-differentiated NETs due to its high sensitivity and specificity for somatostatin receptor expression [8].

In our case, the clear FDG uptake helped localize the lesion and guide the biopsy that led to a definitive diagnosis. This case also adds to the limited body of evidence supporting 18F-FDG PET/CT use in rare breast cancer subtypes.

Neuroendocrine Differentiation in Breast Cancer

The 2019 World Health Organization (WHO) 5th edition categorizes breast NENs into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). [9]

Well-differentiated NETs of the breast typically resemble luminal-type breast cancers, being hormone receptor-positive and HER2-negative. In contrast, poorly differentiated NECs are aggressive, high-grade malignancies, further divided into small cell and large cell types [9].

Diagnosing a primary breast NEN requires a diffuse neuroendocrine marker expression (in > 90% of cells) and comprehensive clinical and radiological exclusion of metastases from extramammary neuroendocrine primaries [10].

A population-based study states that breast NEC accounts for less than 0.1% of all breast cancers and is often underdiagnosed due to overlapping histological and clinical features with conventional subtypes [11]. Breast NENs may present with aggressive behaviour and atypical metastatic patterns, particularly when associated with high-grade features [12].

Immunohistochemical profiling is crucial for accurate diagnosis. Markers such as GATA3 positivity and mammaglobin negativity can help distinguish breast origin from other primary sites. [9]

Limitations

Single case report limits generalizability. Neuroendocrine differentiation contribution to imaging remains speculative; no long-term follow-up.

Clinical Implications

Delayed 18F-FDG PET/CT integration enables earlier metastasis detection in rising markers/ negative imaging, influencing treatment and outcomes.

Conclusion

This case underscores several key learning points: Firstly, the crucial role of nuclear medicine continues to evolve not only with state-of-the-art tracers and technologies but also with techniques and protocols, like delayed-time-point imaging, to optimize the use of current ones. Secondly, delayed PET/CT imaging may be needed to uncover lesions missed on standard-time scans, specifically in cases with high clinical suspicion but inconclusive initial results. Thirdly, rising tumour markers, even non-specific ones like CEA in a breast cancer patient, can be an early and vital clue to recurrence, warranting thorough investigation even when conventional imaging is negative. Finally, breast cancer metastasis with neuroendocrine differentiation, though

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a rare subtype, is an important diagnostic consideration in complex cases, and its detection may be enhanced by optimized imaging protocols.

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the Declaration of Helsinki. As this was a single-case report, ethical review and approval were waived. The Armed Forces College of Medicine Institutional Review Board waived the need for ethics approval.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests: The authors declare that they have no competing interests.

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Availability of data and material: The data presented in this study are not publicly available due to institutional policies but are available on request from the corresponding author, MHM.

Authors' Contributions

Conceptualization, MHM and MTK.; collection of patient data, MHM; contribution to imaging interpretation, MTK, SYW, RAS; performing the histological examination, MME and MAE; writing: original draft preparation, MHM.; writing: review and editing, SYW, YWN, and BEA.; supervision, SYW and RAS. All authors have read and agreed to the published version of the manuscript.

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