Case Report
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Critical Role of Ga-68 DOTATATE PET-CT in a Patient with Neuroendocrine Tumor and Second Primary Cancer

Nöroendokrin Tümörlü ve İkincil Primer Tümörü Olan Hastada Ga-68 DOTATATE PET-BT'nin Kritik Rolü

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Abstract

A 70-year-old female with the diagnosis of the metastatic neuroendocrine tumor was referred to our clinic with new abdominal lymph nodes in computed tomography (CT). This finding was considered as the disease progression, and capecitabine along with temozolomide was added to her current lanreotide therapy. The origin of the new lymph nodes was uncertain due to no response to chemotherapy and the stability of the lymph nodes. ^{68}Ga-DOTATATE PET-CT was performed to resolve the inconsistency in clinical and imaging findings. PET-CT images showed high ^{68}Ga-DOTATATE uptake in abdominal, cervical, left supraclavicular lymph nodes, and few metastatic foci in the liver, which were compatible with a neuroendocrine tumor. Additionally, there were bilaterally enlarged lymph nodes in the neck, axillary, intra-abdominal and inguinal area with no tracer uptake. The incongruent findings of PET-CT suggested a biopsy of non-radio-avid lymph nodes for the possible exclusion of other etiologies. Biopsy revealed that the enlargement of the lymph nodes was caused by small lymphocytic lymphoma (SLL) rather than neuroendocrine metastases. ^{68}Ga-DOTATATE PET-CT led to a critical change in the disease management and confirmed the diagnosis of the secondary tumor with the aid of biopsy. A high radiotracer uptake of neuroendocrine metastases on Ga-68 DOTATATE PET-CT suggested to change the chemotherapy (capecitabine+ temozolomide) to Y-90/Lu-177 DOTATATE therapy, which led to disease stabilization and minor regression. Her newly diagnosed stable SLL was followed accordingly. It can be concluded that ^{68}Ga-DOTATATE PET-CT plays a critical role in the management of patients with neuroendocrine tumors and should be used as a problem solving tool in patients with the discrepancy between clinical and imaging findings.

Keywords: Neuroendocrine tumor; lymphoma; PET-CT; peptide receptor radionuclide therapy; Ga–68 DOTATATE

Özet

Metastatik nöroendokrin tümörü nedeni ile takipte olan 70 yaşındaki hasta, bilgisayarlı tomografi (BT) sinde yeni gelişen abdominal lenf nodları nedeni ile kliniğimize refere edildi. Yapılan değerlendirme sonrası, yeni gelişen lenf nodları hastalık progresyonu olarak kabul edildi ve hastanın tedavisine, kullanmakta olduğu lanreotide ek olarak kapesitabin ve temozolomid eklendi. Ancak, hastanın kemoterapi yanıtı olmadı ve takip görüntülemelerde lenf nodları stabil olarak seyretti. Bu uyumsuz yanıt nedeni ile hastalık varlığını doğrulama ve ileri araştırma yapmak için hastamıza ^{68}Ga-DOTATATE PET-CT yapıldı. PET-BT görüntülerinde abdominal, servikal, sol supraklaviküler lenf nodlarında ve karaciğerde birkaç odakta nöroendokrin tümör metastazı ile uyumlu yüksek ^{68}Ga DOTATATE tutulumu saptandı. Ek olarak; bilateral servikal, aksiller, intraabdominal ve inguinal bölgelerde radyoaktif madde tutulumu göstermeyen büyümüş lenf nodları dikkati çekti. PET-BT'deki uyumsuz bulgular nedeni ile, olası diğer hastalıkların dışlanması amacıyla radyoaktif madde tutmayan lenf nodlarının biyopsisine karar verildi. Yapılan biyopside bu lenf nodlarının nöroendokrin tümörü metastazı olmayıp, küçük lenfositik lenfoma (KLL) ya bağlı olduğu saptandı. ^{68}Ga DOTATATE PET-BT hastamızda doğru yerden biyopsi yapılmasına vesile olarak ikinci tümör saptanmasını sağlamış ve hasta yönetiminde kritik bir değişikliğe yol açmıştır. Ayrıca, PET-BT'de hastamızda nöroendokrin tümör metastazlarında yüksek radyoaktif madde tutulumu görülmesi etkin olmayan kemoterapiden (kapesitabin+temozolomid) vazgeçilip, Y-90-Lu-177 DOTATATE tedavisine geçilmesini sağlamış ve verilen bu yeni tedavi hastalıkta stabilazyon ve minör gerilemeye yol açmıştır. Hasta, yeni tanısı konulan ve stabil seyreden KLL nedeni ile ek takibe alındı. Sonuç olarak, ^{68}Ga DOTATATE PET-BT, hastamızda olduğu gibi nöröendokrin tümörlü hastaların tedavi yönetiminde kritik rol oynamakta olup, klinik ve görüntüleme yöntemlerinin uyumsuzluğunda problem çözücü bir teknik olarak kullanılmalıdır.

Anahtar kelimeler: Nöroendokrin tümör; lenfoma; PET-CT; peptid reseptör radyonüklid tedavi; Ga-68 DOTATATE

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that arise from the cells of the neuroendocrine system. The gastrointestinal tract is the most common site that accounts for 67% of NETs (1). These tumors are commonly diagnosed by endoscopy, computed tomography (CT), or magnetic resonance imaging. Besides, molecular imaging techniques are used to identify unique metabolic and structural differences. Well differentiated NETs tend to grow slowly and have lower metabolic rates. The lower glucose utilization results in lower sensitivity for the detection with fluorodeoxyglucose (FDG) positron emission tomography (PET) (2). NETs are usually well differentiated and demonstrate overexpression of cell surface receptors of somatostatin (mainly SSR2 and SSR5) that enables molecular imaging of NETs with radiolabeled somatostatin analogs (SSR imaging) (3). The superiority of SSR imaging over conventional imaging in NETs has been proved in many clinical situations (4). The major superiority of the SSR imaging is the specificity of the radiotracer to the NETs that enables accurate staging of the disease. Most of the guidelines recommend routine use of abdominal/pelvic multiphasic CT or MRI in staging, though ^{68}Ga-DOTATATE PET-CT (SSR imaging) has been found to be most appropriate. On the other hand, in the follow up only abdominal/pelvic multiphasic CT or MRI is recommended (5). Anatomical imaging modalities have limitations: they are not specific and new structural changes can be evaluated as progression even if they are not associated with the primary disease. In this case report, we emphasize the specificity of ^{68}Ga DOTATATE PET-CT and its value in follow-up in a patient with a previous diagnosis of NET and a new secondary tumor.

Clinical Case

A 70-year-old female with the diagnosis of metastatic NET was referred to our clinic. She had a medical history of previous ileal resection with mesenteric lymph node dissection for ileal NET carried out four years ago. Her NET had a Ki-67 index of 10% with rare mitotic activity (WHO Grade 2). Her post-operative In-111 Octreotide scan showed residual disease foci in the right cervical region, left supraclavicular fossa, and in the para-aortic region, and she was being followed up with Lanreotide therapy for three years.

After three years of the stable disease, CT images showed the development of new abdominal mesenteric, peri-pancreatic, para-aortic, and para-caval lymph nodes (Figure 1: white arrows) in addition to her

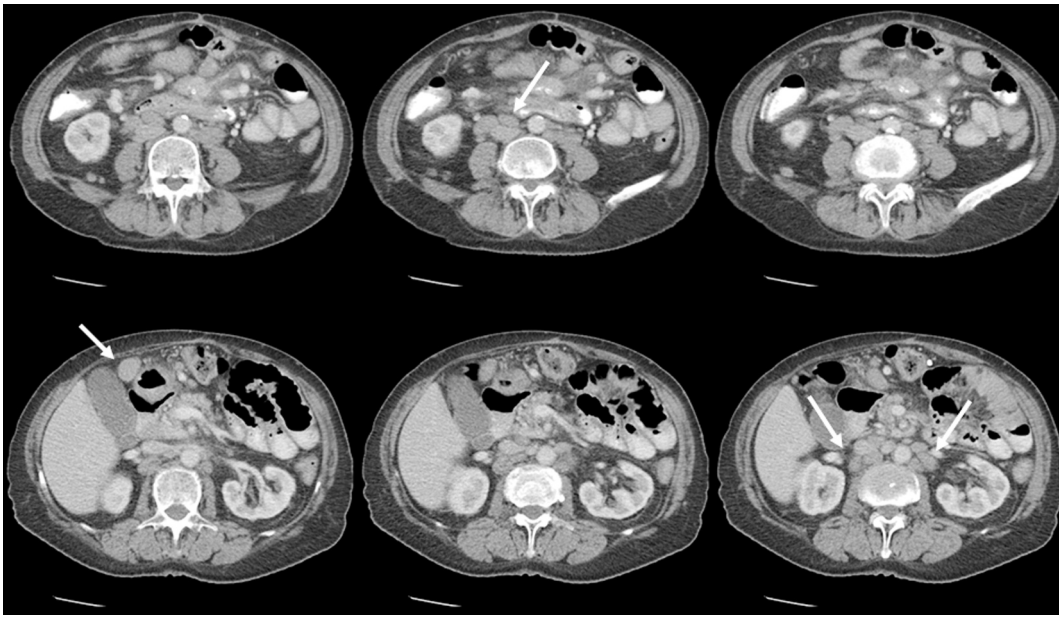

Figure 1: Contrast enhanced CT images showed mesenteric, peri-pancreatic, paraaortic and paracaval lymph nodes (white arrows).

residual disease in the abdomen. This finding was considered as the disease progression, and Capecitabine plus Temozolomide therapy was added to Lanreotide. Despite chemotherapeutic intensification, the size of the lymph nodes showed neither increase nor decrease after six months. ^{68}Ga-DOTATATE PET-CT was performed to unravel the inconsistency in the clinical and imaging findings. PET-CT images showed high Ga-68 DOTATATE uptake in mesenteric, paraaortic, right upper cervical, left supraclavicular, and lymph nodes (SUV max:21) and few foci in liver (Figure 2a: black arrows in maximum intensity projection images, Figure 2b, c: white arrows in low dose CT and fusion PET-CT). Additionally, there were enlarged lymph nodes in bilaterally neck, axillary, intra-abdominal and inguinal spaces which showed no tracer uptake (Figure 2b, c red arrows in low dose CT part of PET-CT). The incongruent findings of PET-CT suggested to carry out the biopsy of non-radio-avid lymph nodes for possible exclusion of other diseases. The biopsy revealed that the enlargement of the lymph nodes was caused by small lymphocytic lymphoma (SLL) rather than neuroendocrine metastases. The chemotherapeutic agents were then stopped, and the patient was followed by the observation for SLL. However, for NET, the patient was referred to the Nuclear Medicine department for radionuclide therapy due to slowly progressing tumor under Lanreotide therapy. Owing to a high radiotracer uptake (SUV max: 21) of neuroendocrine metastases on Ga-68 DOTATATE PET-CT and normal kidney functions, the patient was considered suitable for peptide receptor radionuclide therapy. She received one cycle of 4.4 GBq Y-90 DOTATATE and one cycle of 7.4 GBq Lu-177 DOTATATE therapy (Figure 3a, b). After two cycles, her Ga-68 DOTATATE PET-CT

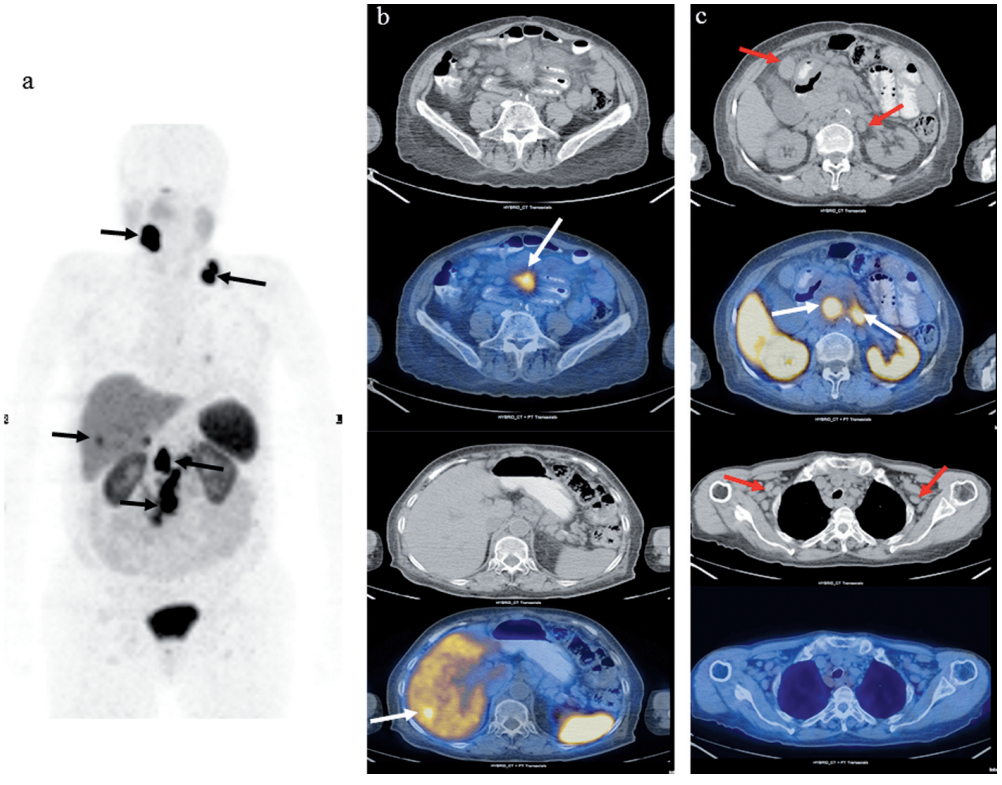

Figure 2: Ga-68 DOTATATE PET-CT images revealed high Ga-68 DOTATATE uptake in mesenteric, paraaortic, right upper cervical, left supraclavicular, lymph nodes (SUV max:21) and few foci in liver (**a:** black arrows in maximum intensity projection images, **b-c:** white arrows in low dose CT and fusion PET-CT). Additionally there were lymph nodes in neck, axillar spaces, intra-abdominal and inguinal bilaterally which show no tracer uptake (b-c red arrows in low dose CT part of PET-CT).

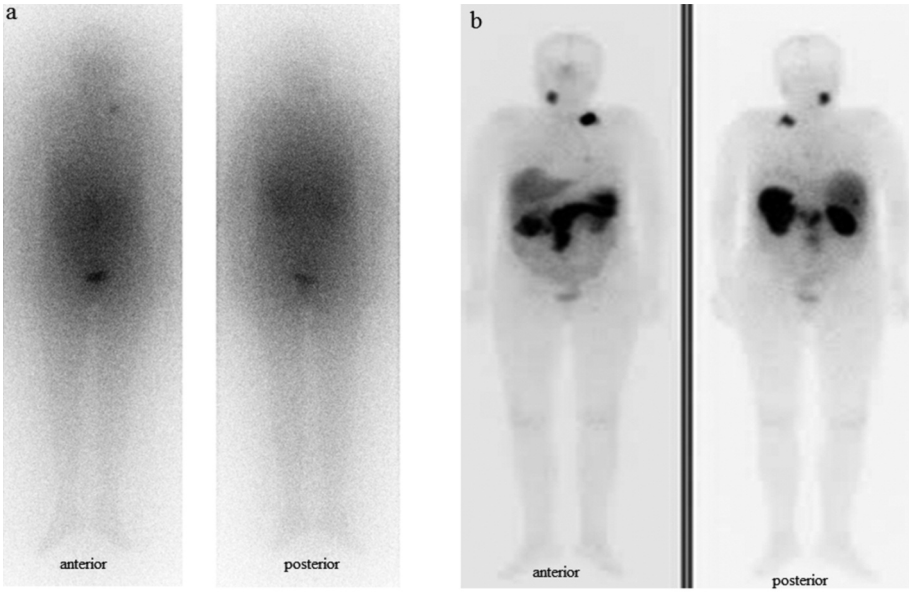

Figure 3: Post therapy bremsstrahlung images after 4.4 GBq Y-90 DOTATATE **(a)** planar whole body post therapy images after one cycle of 7.4 GBq Lu-177 DOTATATE therapy **(b)**. Both scans showed increased uptake in residual disease in neck and abdominal lymph nodes.

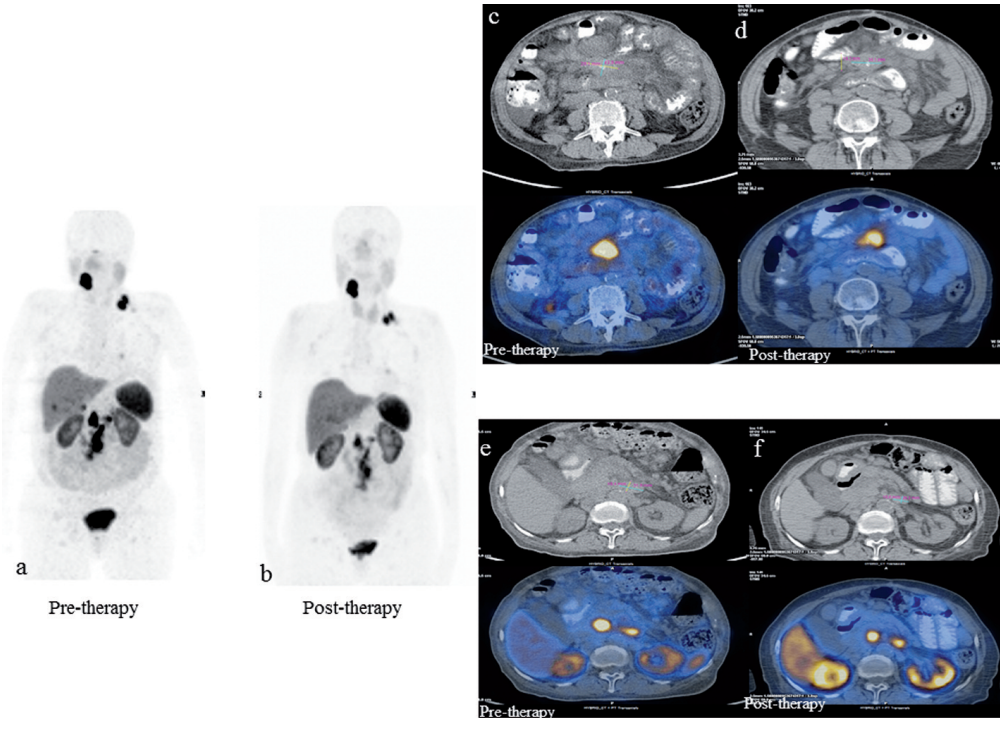

Figure 4: Ga-68 DOTATATE PET-CT was performed after 2 cycles **(b,d,f)** showed decrease in size and tracer uptake of lymph nodes in right neck, left supraclavicular fossa, abdominal lymph nodes and disappearance of foci in liver when compared to pre-therapy scan. **(a,c,e)**. Mesenteric lymph node size decreased from 25x44 mm to 19x34 mm and paraaortic lymph node from 18x21 to 11x20 mm.

(Figure 4 b,d,f) showed a decrease in the size and tracer uptake of lymph nodes in the right neck, left supraclavicular fossa, abdominal lymph nodes and disappearance of foci in the liver compared to the pre-therapy scan (Figure 4 a,c,e).

Discussion

^{68}Ga-DOTATATE PET-CT imaging is the method of choice in the staging of NETs. In a study that evaluated patients with known or suspected neuroendocrine tumors, it showed sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 97%, 95.1%, 96.6%, 98.5%, and 90.4%, respectively (4). Similarly, a meta-analysis found ^{68}Ga-DOTATATE to have an estimated sensitivity and a specificity of 91% (6). The high specificity of the radiotracer is useful as a problem solving tool in situations like diseases that mimic NETs. In our patient, the new lymph nodes were considered as the disease progression with CT. However, no response to therapy and stability of the lymph nodes created suspicion about their origin. Although routine use of ^{68}Ga-DOTATATE is not recommended in the guidelines, this specific tracer could be a helpful tool in suspicious situations like in our patient. ^{68}Ga-DOTATATE PET-CT, in some situations like our case, can lead to a critical change in the management of patients and the diagnosis of the secondary tumor. PET-CT images also offer a possible therapy option by showing a high radiotracer uptake in NET metastases which is essential for effective Y-90/Lu-177 DOTATATE therapy. Clinical impact of Ga-68 DOTATATE PET-CT has also been reported by several groups. The referring physicians reported that Ga-68 DOTATATE led to a change in suspicion of metastatic disease in 24% of the patients (increased in 10% and decreased in 14%) and intended management changes were reported in 60% of patients (7). A recent systemic review and meta-analysis also reported a change in the management after SSTR PET/CT occurring in 44% (range, 16-71%) of NET patients (6).

This case, to the best of our knowledge, is the first report of a patient with NET and secondary cancer as small cell lymphoma. Although the diagnosis of SLL was problematic, it showed relatively indolent behavior and could be followed until several signs of disease progression were seen (like progressive cytopenia, significant disease related symptoms, etc.). Although ^{68}Ga-68 DOTATATE PET-CT has considerable specificity, some benign and malignant entities, like hemangioma and meningioma, may show faint uptakes (8). Though, SLL did not show uptake in our patient, there are few reports of uptake of ^{68}Ga–68 DOTATATE in lymphomas. SSR status was different among lymphoma cell types and SSR expression was higher in Hodgkin's lymphoma of nodular sclerosis subtype and in diffuse large B-cell lymphoma and lowest with SLL (9).

As discussed regarding the clinical effect of ^{68}Ga–68 DOTATATE PET-CT, this modality not only solved the diagnostic dilemma but also offered new therapy options. Peptide receptor radionuclide therapy (PPRT) is a novel therapy option for patients showing a high degree of SSR expression as detected by ^{68}Ga-68 DOTATATE PET-CT. Phase 3 randomized controlled NETTER-1 trial for midgut NETs provided strong evidence for PPRT in patients with midgut NET (10). The patients with a high degree of uptake in PET scans, when given Lu-177 octreotate therapy compared to high dose octreotide, show a better progression-free overall survival rate. Similarly, our patient with mild progression received Y-90 and Lu-177 octreotate sequentially and showed a minor response. Finally, ^{68}Ga-DOTATATE PET-CT plays a critical role in the management of patients with neuroendocrine tumors and should be used as a problem solving tool in patients with the discrepancy between clinical and imaging findings.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Tuğçe Telli, Murat Tuncel, Saadettin Kılıçkap; Design: Murat Tuncel, Saadettin Kılıçkap; Control/Supervision: "Murat Tuncel, Saadettin Kılıçkap; Data Collection and/or Processing: Tuğçe Telli, Murat Tuncel; Analysis and/or Interpretation: Tuğçe Telli, Murat Tuncel; Literature Review: Tuğçe Telli, Murat Tuncel, Saadettin Kılıçkap; Writing the Article: Tuğçe Telli, Murat Tuncel, Saadettin Kılıçkap; Critical Review: Murat Tuncel; References and Fundings: Murat Tuncel, Saadettin Kılıçkap; Materials: Murat Tuncel, Saadettin Kılıçkap.

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