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# Reactive Lymph Nodes: A diagnostic challenge in Somatostatin Receptor Imaging of Neuroendocrine Neoplasms

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## ABSTRACT

**Background**: Reactive lymph node changes can present significant diagnostic challenges, particularly in patients with neuroendocrine neoplasms.

Objectives: To investigate the phenomenon where reactive lymph nodes, which are typically benign, mimic the appearance of lymph nodes positive for 68Ga-DOTATOC-PET or SRS.

**Methods**: Two patients with a history of with neuroendocrine tumors were subjected to DOTATOC-PET, histopathological examination and immunohistochemical analyses. Detailed clinical histories were collected, and the lymph nodes underwent thorough histopathological evaluations to determine the underlying cause of the imaging findings.

**Results**: Both neuroendocrine neoplasms cases exhibited marked hyperplasia of follicular dendritic cells (FDCs) in the lymph node germinal centers, forming dense somatostatin receptor 2 (SSTR2)-positive meshworks. The SSTR2 on these cells binds 68Ga-DOTATOC, leading to imaging appearances that may mimic metastatic lymph nodes. In one case, the changes were associated with COVID-19 vaccination, and in the other, with chronic pelvic inflammation.

**Conclusions**: Understanding the phenomenon of DOTATOC-PET positivity due to reactive follicular dendritic hyperplasia is crucial for the accurate interpretation of PET scans in neuroendocrine neoplasm patients. This awareness helps avoid misdiagnosis and unnecessary interventions, highlighting the importance of correlating imaging findings with clinical history and performing thorough histopathological evaluations.

***Keywords:*** *Neuroendocrine tumors, DOTATOC-PET, Follicular dendritic cells, Somatostatin receptor 2, Reactive lymphadenopathy, Pitfalls*

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## 1. INTRODUCTION

Neuroendocrine neoplasms are a diverse group of tumors arising from neuroendocrine cells in various organs. While they commonly present in the bronchopulmonary system, gastrointestinal tract, and pancreas, their occurrence at other sites is less frequent. Combining computed tomography (CT) and somatostatin receptor scintigraphy (SRS) enhances diagnostic accuracy and facilitates the monitoring of these tumors. Dotatoc PET is an important assay for staging neuroendocrine tumors and detecting metastatic lymph nodes. Dotatoc is a 68Ga-labeled DOTA-D-Phe1-Tyr3-Octreotide (68Ga-DOTATOC) that is used in PET scans to label neuroendocrine tumors and their metastases by binding to somatostatin receptors (SSTR) [1]. These receptors are G-protein-coupled receptors expressed on the cell membrane of neuroendocrine cells and tumors derived from them (NET G1, G2, or G3), pheochromocytoma, and other cell types such as follicular dendritic cells, Merkel cells in the skin, and meningeal cells [2]. Activation of these receptors by somatostatins or synthetic analogs leads to the dissociation of the G-protein molecule, which regulates cell growth and hormone secretion in cells

bearing these receptors [3].

However, reactive lymph node changes, mainly triggered by immune responses to infections, vaccination, or other inflammatory processes, may also show increased uptake of 68Ga-DOTATOC on PET scans [4]. This can result in a false DOTATOC-positive imaging appearance, suggesting the presence of metastatic disease in neuroendocrine neoplasms, whereas these lymph nodes are reactive rather than neoplastic. In general, correlating with the patient's medical history and clinical symptoms is essential for correctly interpreting imaging findings. In many cases, additional imaging modalities or biopsy of suspicious tissue may be necessary to confirm the nature of lymph node involvement.

The current work investigated false-positive 68Ga-DOTATOC-avid lymph nodes in patients with neuroendocrine tumors, with the aim of elucidating this phenomenon based on histopathological and immunohistochemical examination of related lymph nodes.

## 2. MATERIALS AND METHODS

**Patient Selection**
Two female patients, aged 83 and 79 years, with a histopathologically confirmed history of pulmonary neuroendocrine tumors were included in this study. In both cases, $^{68}$Ga-DOTATOC PET/CT imaging, performed according to the standard protocols [5], identified radiotracer-avid lymph nodes that were radiologically suspicious for metastatic disease.
Histopathological and Immunohistochemical Analysis

The DOTATOC-avid lymph nodes were surgically excised for definitive diagnosis. The specimens were subjected to a comprehensive histopathological workup. The lymph nodes were sectioned at multiple levels. Sections for conventional histological analysis were stained with hematoxylin and eosin (H&E) and examined by light microscopy.
Concurrently, serial sections were prepared for immunohistochemical (IHC) characterization. Different sets of primary monoclonal antibodies were applied. They include Pan-Cytokeratin (MNF116, Dako) as an epithelial marker, Chromogranin (LK2H10, Sigma-Aldrich) as a neuroendocrine marker, Somatostatin Receptor 2 (clone EP149, Sigma-Aldrich), and CD21(ZM75, Thermo-Fisher) and CD23 (1B12, Sigma-Aldrich) as markers for follicular dendritic cells.

IHC staining was performed automatically on a DAKO LINK 48 auto stainer using a standard protocol involving a polymer-based detection system with DAB chromogen and hematoxylin counterstaining.

**Results**
**Case presentation:**
**Case 1: 83-year-old female with Atypical Carcinoid**
A $^{68}$Ga-DOTATOC PET/CT scan revealed an enlarged, radiotracer-avid right axillary lymph node, considered highly suspicious for metastasis (Fig. 1). Histopathological examination of the excised node revealed marked lymphoid follicular hyperplasia with progressive transformation of the germinal centers (Fig. 2 & 3). IHC demonstrated a dense three-dimensional meshwork of SSTR2-positive follicular dendritic cells (Fig. 4, 5, 6 & 7). Stains for Pan-cytokeratin and Chromogranin were negative, confirming the absence of metastasis. Additional history revealed a COVID-19 vaccination in the right arm six months prior. The patient subsequently underwent a left upper lobe lobectomy, which confirmed a pT3 pN1 R0 G2 atypical carcinoid with hilar node metastases.

**Case 2: 79-year-old female with incidental NET G1**
Following a partial lung resection for an aspergilloma, which incidentally revealed a 5mm NET G1 (pT1a, Nx, R0), a staging DOTATOC-PET was performed. It showed intense uptake (SUVmax 10.83) in enlarged inguinal and para-iliacal lymph nodes (Fig. 8). Due to the unusual location, a lymph node was excised. Histology revealed follicular hyperplasia with sinus histiocytosis (Fig. 9 & 10). IHC again showed marked proliferation of SSTR2-positive, CD23-positive FDCs (Fig. 11 & 12). No metastatic tissue was identified. The reactive changes were attributed to chronic inflammation in the pelvic region.

**Results**
An enlarged 68Ga-DOTATOC avid right axillary lymph node was detected, which considered highly suspicious for metastases of the atypical carcinoid (Fig.1). Two weeks later, a right-sided axillary lymphadenectomy was initially performed to inspect the suspicious atypical lymph nodes to confirm the PET diagnosis or to rule out other types of malignancy, such as lymphoma or occult breast carcinoma. The histopathological examination of this axillary lymph nodes revealed marked lymphoid follicular hyperplasia with progressive transformation of the germinal centers at various stages (Fig. 2 & 3). The immunohistochemical examination using specific antibodies against follicular dendritic cells CD21, CD23, and somatostatin receptor 2 also confirmed this marked follicular dendritic cell hyperplasia within the germinal

centers (Fig. 4 & 5), which appear to form a three-dimensional meshwork of somatostatin receptor 2-positive follicular dendritic cells (Fig. 6 & 7). In the serial H&E sections and immunohistochemistry (Pan-cytokeratin and Chromogranin), no metastatic tissue of a neuroendocrine tumor or epithelial neoplasia was detected. Additional clinical history from this particular case revealed a COVID vaccination administered in the right arm 6 months prior to the Dotatoc-PET. Three weeks later, the patient underwent left upper lobe lobectomy with lymphadenectomy. The diagnosis was confirmed by histopathology, which revealed two separate tumors within the upper lobe measuring 37 and 10 mm, along with two hilar lymph node metastases. The tumor was then staged as pT3, pN1 (1/7), R0, G2.

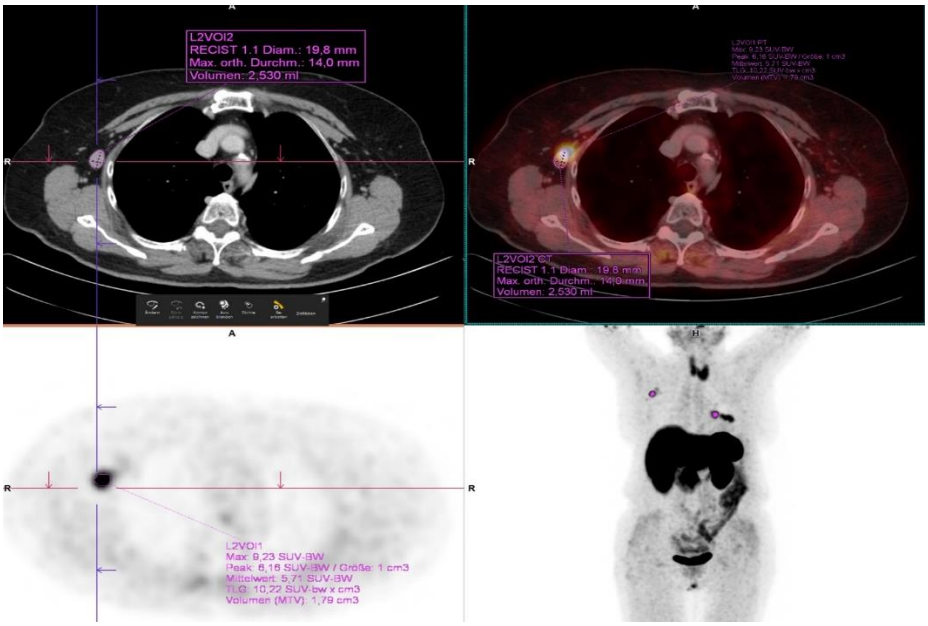


**Figure 1: 68Ga-Dotatoc-PET/CT of an 83 years old woman. Ga-Dotatoc avid somatostatin receptor-positive solid tumor in left upper lobe and left hilar lymph node metastasis. The CT, axial fused, PET and Maximum Intensity Projection (MIP) shows PET-positive right sided axillary lymphadenopathy.**

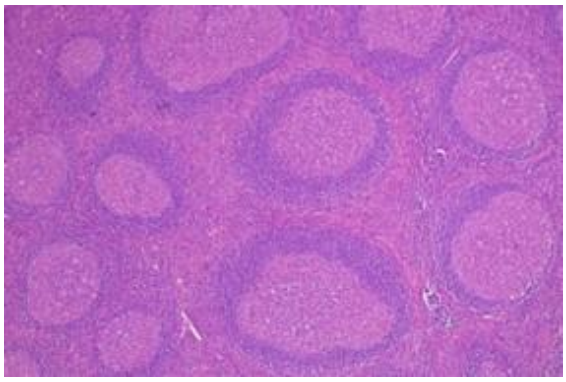

**Figure 2: H&E section from the lymph node (40X) exhibiting follicular hyperplasia with secondary lymphoid follicles and progressive transformation of the germinal centers.**

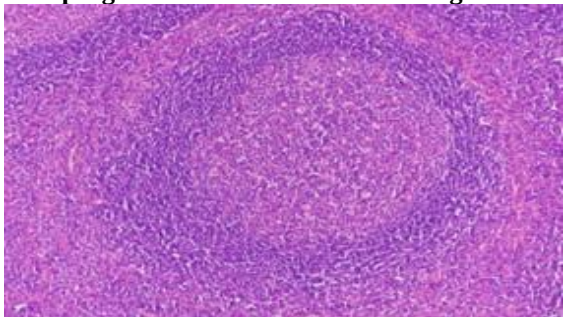

**Figure 3: H&E section from the lymph node (100X) showing activated germinal center with progressive transformation of the germinal center.**

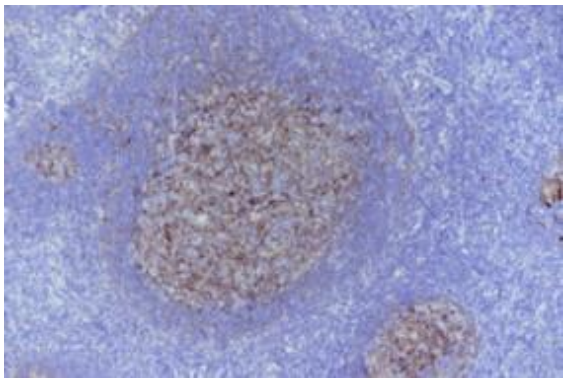

**Figure 4: CD21 immunostain exhibiting germinal centers with follicular dendritic cell hyperplasia (100X).**

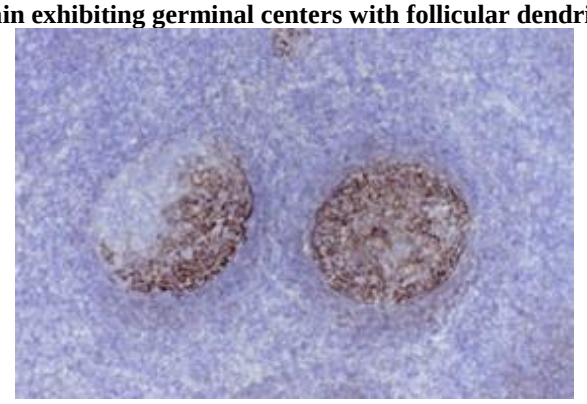

**Figure 5: CD23 immunostain shows further germinal centers with follicular dendritic cell hyperplasia (100X).**

**Figure 6: SSTR2 immunostain reveals marked proliferation of follicular dendritic cell (100X)**

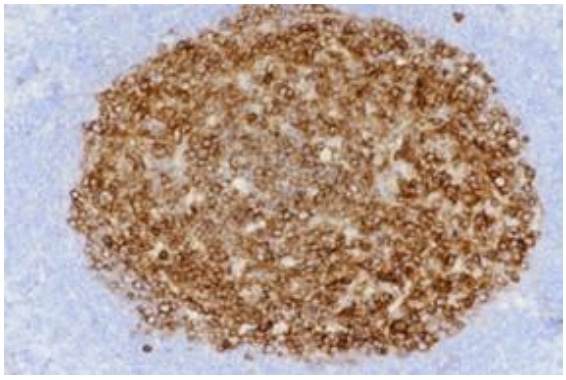

**Figure 7: SSTR2 immunostain showing marked follicular dendritic cell hyperplasia in a hyperplastic germinal center (200X).**

The second case involves a 79-year-old female patient who had a lesion in the upper lobe of the left lung on CT scan, which was suspicious for aspergilloma. No pathological lymph nodes were observed on the CT scan. The patient underwent partial resection of the upper lobe, and the clinical diagnosis was confirmed by histopathological examination. In the same

specimen, a small completely resected carcinoid (NET G1) measuring 5 mm was also detected. The tumor was positive for Chromogranin, Somatostatin receptor 2, and OTP. This tumor was staged as pT1a, Nx, R0, G1 NET. For tumor staging and follow-up, Dotatoc-PET was performed 8 weeks later, which revealed enlarged inguinal and para-iliacal lymph nodes with intense uptake of 68Ga-DOTATOC (SUV max 10.83). This finding was primarily diagnosed as lymph node metastases of the known pulmonary endocrine tumor (Fig. 8). Because of the unusual localization of lymph node metastases, the tumor board required histopathological confirmation of the metastases. A large inguinal lymph node was resected and sent for histopathological examination. Multiple sections from the lymph node revealed follicular hyperplasia with activated germinal centers and sinus histiocytosis (Fig. 9 & 10). The germinal center showed marked proliferation of CD23-positive follicular dendritic cells, which also exhibited a strong expression of somatostatin receptor 2 (Fig. 11 & 12). Similar to the first case, conventional H&E histology and immunohistology with Pan-cytokeratin and Chromogranin showed no metastatic tissue of an epithelial or neuroendocrine tumor.

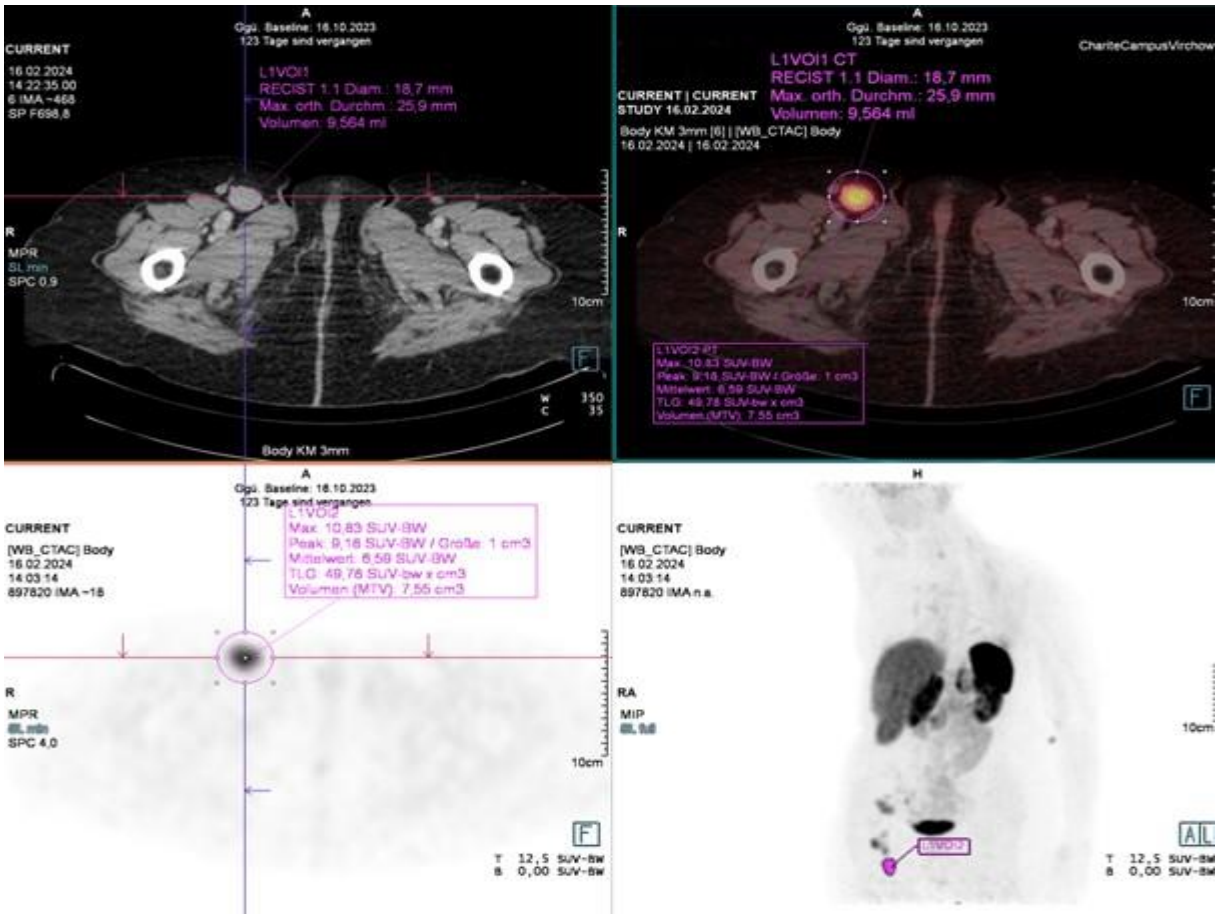


**Figure 8: 68Ga-Dotatoc-PET/CT of a 79 years old woman after lingula resection with NET G1. The CT, coronal fused, PET and Maximum Intensity Projection (MIP) demonstrate PET-positive right sided inguinal lymphadenopathy.**

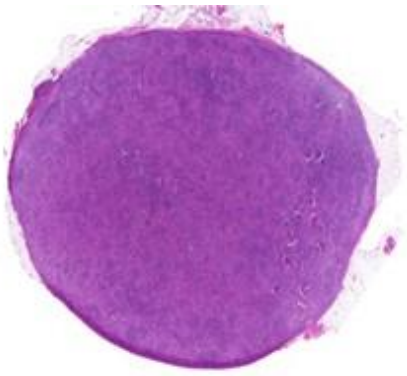

**Figure 9: Enlarged inguinal lymph node with follicular hyperplasia and sinus histiocytosis (10X).**

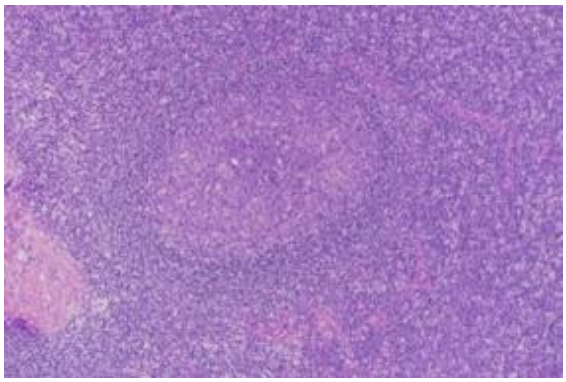

**Figure 10: The lymph node shows large lymph follicles with activated germinal centers**

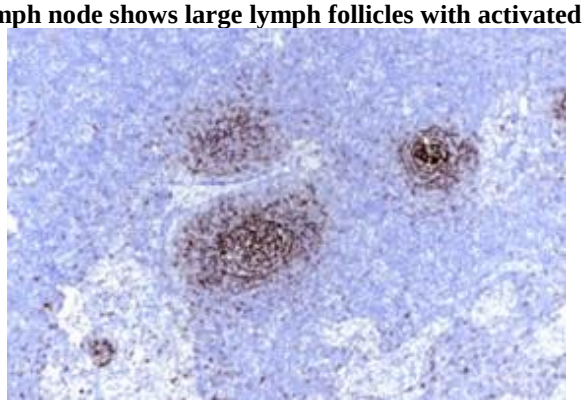

**Figure 11: CD23 immunostain showing marked proliferation of follicular dendritic cells within reactive germinal centers.**

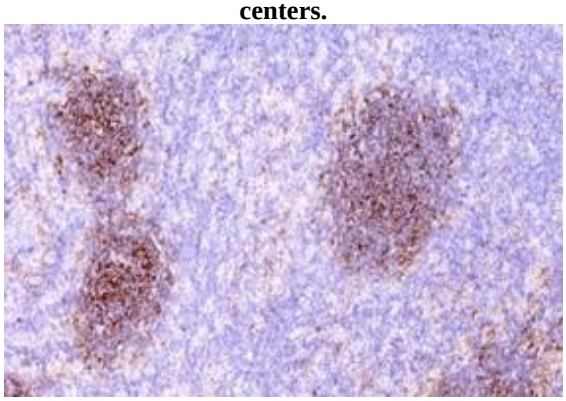

**Figure 12:The follicular dendritic cells with strong SSTR2 expression.**

## DISCUSSION

Neuroendocrine neoplasms are a diverse group of tumors arising from neuroendocrine cells in various organs. While they commonly present in the bronchopulmonary system, gastrointestinal tract, and pancreas, their occurrence at other sites is less frequent. Combining computed tomography (CT) and somatostatin receptor scintigraphy (SRS) enhances diagnostic accuracy and facilitates the monitoring of these tumors. Nevertheless, enlarged reactive lymph nodes may exhibit pronounced tracer uptake, mimicking metastatic involvement, which can complicate image interpretation [6].

Imaging plays a pivotal role in the evaluation of primary site, staging, planning surgical strategies, and in the diagnosis of recurrences and/or distant metastases after treatment of neuroendocrine neoplasms. SRS is one of the most widely used methods for accurately localizing tumors originating from the neuroendocrine system, as they universally possess specific receptors for somatostatin [7]. PET/CT imaging with 68Ga- DOTATOC was crucial in identifying the affected lymph nodes as suspicious for metastasis due to their high uptake values. The maximum standardized uptake value (SUVmax) for the identified lymph nodes was significantly elevated, prompting further histopathological investigation. The imaging findings were consistent with previous studies indicating the high sensitivity of 68Ga-DOTATOC PET/CT in detecting neuroendocrine tumor metastases, though false positives due to reactive follicular hyperplasia were noted [1, 8, 9].

False-positive 68Ga-DOTATOC uptake in lymph nodes is increasingly recognized in the oncologic imaging literature and

aligns with our two cases in which intense nodal avidity reflected reactive follicular hyperplasia rather than metastatic neuroendocrine tumor (NET). The high sensitivity of somatostatin receptor positron emission tomography (SSTR–PET) for NET staging is well established, but several series and case reports underscore interpretive pitfalls in inflammatory or lymphoproliferative conditions. Sharma et al. and Sanli et al. detail the excellent detection characteristics of SSTR–PET while acknowledging non-neoplastic etiologies of uptake that may confound specificity [1, 10]. Similarly, Srirajaskanthan et al. showed that 68Ga agents outperform 111In-octreotide in detecting disease, yet background SSTR expression in non-NET tissues can still yield unexpected foci [9].

Mechanistic data support our histopathologic observations. Follicular dendritic cells (FDCs) form three-dimensional networks within germinal centers that capture and present antigen to B cells [11, 12]. Tao et al. demonstrated that SSTR2a is a robust immunohistochemical marker for FDCs and FDC-related tumors, providing a biologic basis for SSTR–PET avidity in reactive follicles rich in FDC meshworks[13]. In both of our cases, dense SSTR2-positive FDC proliferation explained strong DOTATOC uptake despite the absence of metastatic neuroendocrine cells on serial H&E and immunostains.

The literature offers convergent clinical correlates that mirror our patients. First, vaccine-associated lymphadenopathy can be SSTR–PET–avid: Pudis et al. reported 68Ga-DOTATOC–avid lymphadenopathy following mRNA COVID-19 vaccination, emphasizing the need to incorporate recent immunization history into image interpretation [4]. Our first case, with ipsilateral recent vaccination and axillary reactivity, is concordant with these findings. Second, chronic inflammatory states can drive reactive nodal hyperplasia with prominent FDC networks; our second case, with pelvic inflammatory history and avid inguinal nodes, reflects this paradigm [11, 12].

In both cases, no metastatic tissue from the previously diagnosed neuroendocrine tumors was detected by conventional H&E histopathology or immunohistochemistry. However, marked hyperplasia of the follicular dendritic cells was observed in the germinal centers of the lymph nodes in both cases, forming a dense three-dimensional meshwork of somatostatin receptor 2-positive follicular dendritic cells. After further investigation of the clinical history for these patients, it was concluded that the changes in the first case may have been a result of Covid vaccination, whereas in the second case, they may have been due to chronic inflammation in the pelvic organs.

Follicular dendritic cells are immune accessory cells found in the germinal centers of primary and secondary lymphoid follicles in lymph nodes, spleen, and mucosa-associated lymphoid tissue [14]. They form a three-dimensional meshwork that maintains the follicular architecture and play a crucial role in presenting antigens to the surrounding B cells [14]. They also produce chemokines that attract B cells and other immune cells to the germinal centers, facilitating effective immune surveillance and response [11, 12]. 68Ga-DOTATOC binds to the somatostatin receptor type 2 located on the membranes of activated follicular dendritic cells within the affected lymph nodes [13]. This binding results in an extensive imaging appearance that may mimic metastatic lymph nodes in patients with neuroendocrine tumors [10, 13].

Similarly, neoplastic processes associated with follicular dendritic cell hyperplasia, including Castleman disease and various types of lymphoma, have been described to exhibit 68Ga-DOTATOC avid PET features (Fig. 13-17) [15-17]. Accordingly, primary neoplasms of follicular dendritic cells such as follicular dendritic cell sarcoma are likely to exhibit 68Ga-DOTATOC avid PET appearance, but we did not find any case in the literature demonstrating 68Ga-DOTAOC positivity in this rare malignancy.

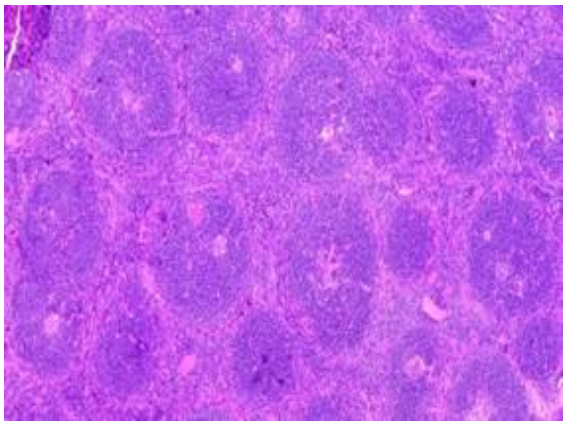

**Figure 13: Castleman disease exhibiting germinal center hyperplasia, with follicular dendritic cell hyperplasia**

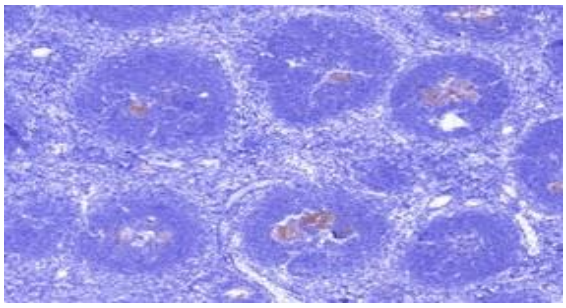

**Figure 14: The hyperplastic germinal centers with follicular dendritic cell hyperplasia in Castleman disease exhibiting strong SSTR2 expression (SSTR2 immunostain).**

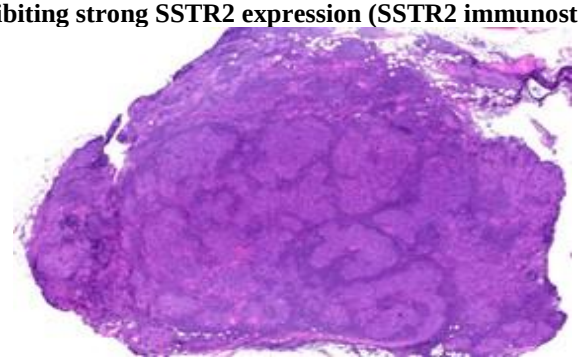

**Figure 15: Follicular lymphoma (cervical lymph node) with neoplastic follicles.**

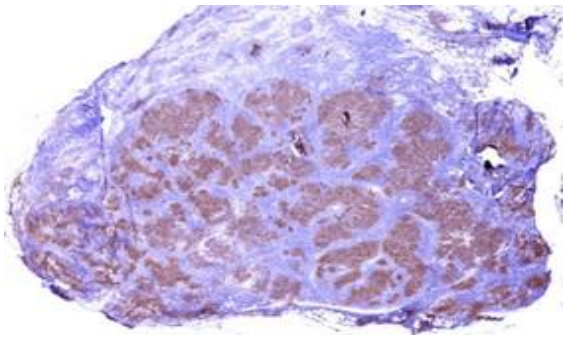

**Figure 16.: The neoplastic follicles in follicular lymphoma showing marked proliferation of SSTR2 positive follicular dendritic cells (SSTR-2 immunostain)**

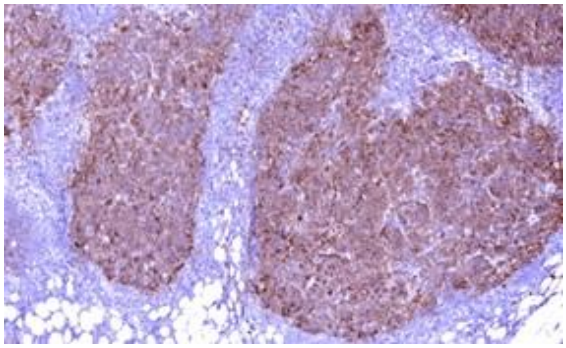

**Figure 17: large magnification of neoplastic follicles with prominent SSTR-2 positive follicular dendritic cells.**

In conclusion, the interpretation of reactive lymph node changes in patients undergoing Dotatoc-PET is challenging because these changes can resemble Dotatoc-PET positive lymph nodes and thus mimic nodal metastasis. As a consequence, once lymphadenopathy is seen on CT, a precise radiological examination is necessary in order to ensure an accurate diagnosis. Reactive lymph nodes draining areas with chronic inflammation or those adjacent to vaccinated sites in addition to lymph nodes with lymphoproliferative disorders may exhibit Dotatoc-PET positivity in patients with neuroendocrine tumors. This can be attributed to reactive follicular dendritic hyperplasia in activated germinal centers or neoplasms associated with follicular dendritic cell hyperplasia. The observed FDC hyperplasia and their strong SSTR2 expression likely contributed to the false-positive PET/CT results, highlighting the need for histopathological confirmation

to differentiate between true metastatic involvement and reactive changes [18].

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