



# A Strange Case of Phyllodes Tumor Detected Using $^{18}\text{F}$ -FDG PET/CT in an Adolescent Patient Affected by Hodgkin Lymphoma: A Possible Pitfall

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## Clinical Practice Points

- A 15-year-old girl presented with asthenia, fever, night sweats, and supraclavicular swelling.
- Ultrasonography (US) revealed left-sided neck and supraclavicular lymphadenopathies. Positron emission tomography (PET)/computed tomography (CT) demonstrated 18-fluorine-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) uptake in several lymph nodes of the left laterocervical, supraclavicular, deep axillary, supraclavicular, retropectoral and mediastinal regions, and in the right mammary gland.
- Biopsy of the left supraclavicular lymph node revealed Hodgkin lymphoma (HL).
- Two days later, US-guided core biopsy of the breast led to the diagnosis of phyllodes tumor.
- In the PET/CT scan for reevaluation of HL after 2 cycles of chemotherapy, the abnormal lymph node findings had disappeared, and the  $^{18}\text{F}$ -FDG avidity in the right mammary gland persisted.

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## Introduction

Phyllodes tumors of the breast are biphasic neoplasms consisting of an epithelial component and a predominant and more cellular fibrotic one.<sup>1,2</sup> In 1838, Johannes Muller was the first to call them with the name of Greek origin “cystosarcoma phyllodes,” because they are characterized by singular leaf-like aspects extending toward cyst-like spaces with complete envelopes.<sup>1,2</sup> Even if both of the components could be neoplastic, the stromal one with its spindle

cells (fibroblasts and myofibroblasts) definitely determine the behavior of the tumor.<sup>2,3</sup>

These neoplasms are rare, accounting for only 0.3% to 1.5% of all breast tumors and for 2.5% of all fibroepithelial lesions of the breast.<sup>2,3</sup> Phyllodes tumors usually affect women and only few cases were found in men. The peak incidence in women is between 35 and 55 years, predominantly between 45 and 49 years, and the malignant cases are more frequently seen in older ages than the benign ones.<sup>2,4</sup> The aggressive cases represent less than 0.5% of all breast malignancies.<sup>5</sup>

In general, breast nodules are rare in adolescents and they usually are fibroadenomas. Even if uncommon, sometimes phyllodes tumors can occur even at this age and, considering their malignant potential and the high rate of recurrence, a correct differential diagnosis versus the more frequent benign fibroadenomas is an issue of primary importance and also of particular difficulty.<sup>4</sup>

Here we present a very rare case of phyllodes tumor that occurred in an adolescent female patient affected by Hodgkin lymphoma (HL), first detected with 18-fluorine-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET)/computed tomography (CT),

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and describe the role of PET/CT in the diagnosis and in the subsequent clinical management.

### Case Report

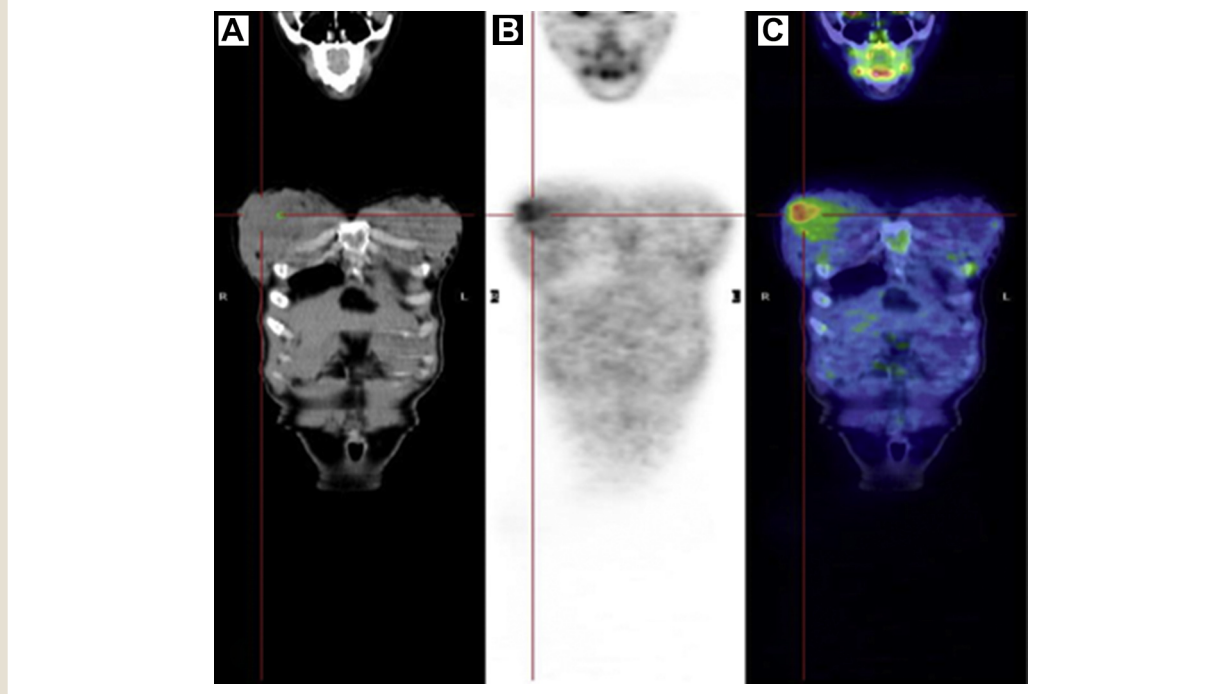
A 15-year-old girl was referred by a pediatrician to our PET center at the end of May 2013 who presented with a systemic syndrome with mild hyperemia in the pharynx, asthenia, fever, night sweats, weight loss (approximately 3 kg in 3 weeks) and supraclavicular swelling. She also had neutrophilia, mild anemia, and increased erythrocyte sedimentation rate, C reactive protein, and serum L-lactate dehydrogenase. Chest x-ray (CXR) showed bilateral widening of the mediastinum possibly related to lymphadenopathy. In addition, ultrasonography (US) revealed some increase in size of lymph nodes in the left side of the neck and bilaterally in the supraclavicular regions, with the largest (3.5 cm maximum diameter) conglomerated on the left. No abnormalities were found in US of the abdomen.

The patient underwent microbiological tests for Epstein-Barr virus, adenovirus, cytomegalovirus, and Bartonella, that were all negative. An  $^{18}\text{F}$ -FDG PET/CT scan was requested to characterize the lymph node findings. It was performed from the base of the skull to the proximal thighs, using an integrated PET/CT device (Discovery ST-E, General Electric Medical Systems, Milwaukee, WI), approximately 60 minutes after the intravenous administration of  $^{18}\text{F}$ -FDG (296 MBq). The patient had fasted for 8 hours

before the injection. PET data were acquired in 3-D mode on a matrix of  $128 \times 128$  pixels. Low-dose CT (tube voltage = 80 kVp, tube current = 60 mA, pitch of helical = 3.75:1) was performed for attenuation correction and anatomical localization of the PET signal, and images were acquired on a matrix of  $512 \times 512$  pixels. The  $^{18}\text{F}$ -FDG PET/CT study demonstrated multiple hypermetabolic lymph nodes in the left laterocervical and supraclavicular (maximum standardized uptake value [SUVmax], 10.48) and deep axillary regions, in the right supraclavicular (SUVmax, 10.98) and retropectoral regions (SUVmax, 3.2), and in all the mediastinal lymph nodes (SUVmax, 13). Diffuse  $^{18}\text{F}$ -FDG distribution was observed in the pharynx, in keeping with flogosis evidenced at clinical examination. Intense  $^{18}\text{F}$ -FDG uptake was found in the spleen and in the skeleton, with these findings likely related to aspecific activation. There was also an increased focal  $^{18}\text{F}$ -FDG uptake in the right mammary gland with SUVmax of 2.38; ratio of tumor SUVmax to normal liver SUVmax was 1.72, whereas primary tumor to SUVmax blood pool ratio was 0.94 (Figure 1). A bone marrow aspiration and a bone marrow biopsy were performed and resulted negative. A further biopsy of the left supraclavicular lymph node conglomerate was performed and revealed HL.

A couple of days later, US of the breasts demonstrated a big nodule (5 cm maximum diameter), with net margins and hypervascularization at Doppler examination, situated in the right upper lateral quadrant and in the axillary tail, consistent with secondary

**Figure 1** An  $^{18}\text{F}$ -FDG PET/CT Scan Performed After 2 Cycles of Chemotherapy for Hodgkin Lymphoma. Coronal Views of (A) CT, (B) PET, and Fused (C) PET/CT Scans. A Focus of Abnormal  $^{18}\text{F}$ -FDG Uptake (SUVmax, 2.38; TSUVmax/LSUVmax, 1.72; TBR, 0.94), Already Present at the Baseline  $^{18}\text{F}$ -FDG PET/CT Scan (Not Shown), Persisted in the Right Mammary Gland. Histological Examination After Surgery of the Breast Proved Evidence of Phyllodes Tumor



Abbreviations: CT = computed tomography;  $^{18}\text{F}$ -FDG = 18-fluorine-fluorodeoxyglucose; LSUVmax = liver SUVmax; PET = positron emission tomography; SUVmax = maximum standardized uptake value; TBR = tumor to SUVmax blood pool ratio; TSUVmax = tumor SUVmax.

localization of HL or with the presence of fibroadenoma. Afterward, the pediatrician examined the breast of the girl and identified a palpable mass within the right mammary gland. At the clinical examination the patient did not refer to any symptoms related to the breast mass. A US-guided core biopsy was requested and led to a diagnosis of low grade phyllodes tumor with mild stromal hypercellularity, mild atypia, and no evidence of necrosis.

Because of the major concerns that arose from the diagnosis of HL, the surgical procedure for removal of the phyllodes tumor was postponed and the girl was referred for treatment of HL. The girl started antibiotic therapy with progressive reduction of the inflammation indexes and chemotherapy with 6 cycles of COPP/ABV (cyclophosphamide, vincristine, procarbazine, prednisolone/adriamycin, bleomycin, vinblastine; protocol Associazione Italiana di Ematologia e Oncologia Pediatrica - Hodgkin Lymphoma 2004). After 1 cycle of chemotherapy CXR and neck US showed reduction of the mediastinum widening and decrease in size of the hypochoic lymph nodes, respectively.

In the PET/CT scan for reevaluation of HL, after 2 cycles of chemotherapy, the abnormal lymph node findings had disappeared, and the increased <sup>18</sup>F-FDG avidity previously reported in the right mammary gland persisted (Figure 2). A further <sup>18</sup>F-FDG PET/CT scan was performed after 4 cycles of chemotherapy and also resulted as negative.

At the end of chemotherapy, in consideration of the core biopsy findings suggesting a low aggressiveness pattern, the patient underwent surgery (wide quadrantectomy) of the right breast. The histological examination proved evidence of benign phyllodes tumor with low mitotic rate, regular margins and low propensity to tissue invasion (5 × 4 × 3 cm, cytokeratin 5/6 negative, Ki-67 proliferation: 2%).

Finally, the last PET/CT, performed 2 months after surgery, confirmed the HL complete response to treatment and revealed a

slightly heterogeneous <sup>18</sup>F-FDG distribution in the right breast consistent with postsurgical changes.

## Discussion

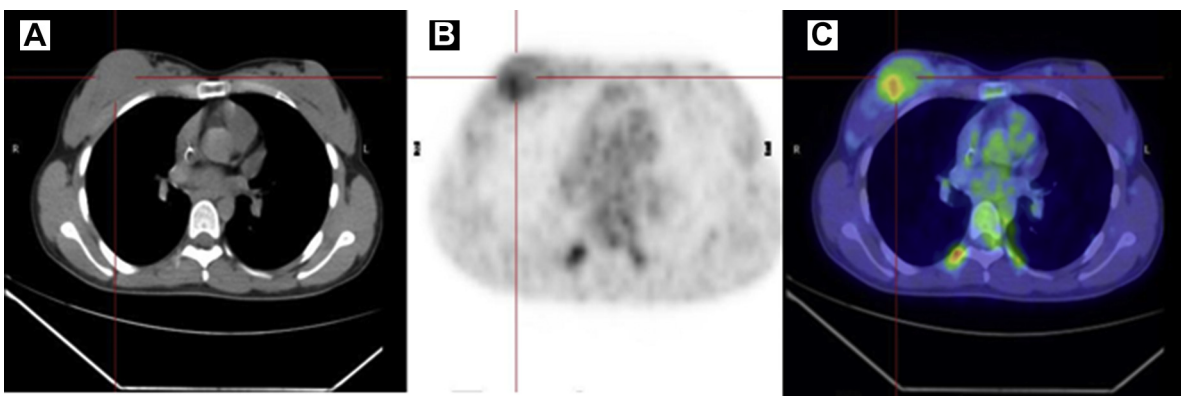
Phyllodes tumors of the breast are relatively infrequent, especially in childhood and adolescence<sup>6</sup> and a few reports are found in literature.<sup>7-11</sup> Our exceptional case suggests that a phyllodes tumor might grow even in a young mammary gland and should be taken into account in the differential diagnosis of breast nodules occurring at this age.

In 1982, the World Health Organization classified phyllodes tumors in 3 grades: benign, borderline, and malignant, according to some histopathological aspects of their stromal component, such as degree of cellular atypia, mitotic activity per 10 high power fields, and degree of stromal overgrowth, but also tumor necrosis and margin appearance.<sup>2-4,12</sup> Malignant cases can cause distant metastases with hematological spread usually to lungs, bone, and brain (and in rare instances also liver or heart). Lymph node involvement is very uncommon. Fortunately, most phyllodes neoplasms are benign (54%), in particular in young patients, the borderline and malignant tumors accounting for 12% and 30% of all cases, respectively.<sup>4,12</sup> The most aggressive lesions usually affect patients in the older age group.<sup>2</sup>

Contrary to the much more frequent fibroadenomas, phyllodes tumors are characterized by a high rate of local recurrences, which are seen especially in case of malignant lesions. Recurrences are generally related to a too-conservative surgical procedure and positivity of the surgical margins. Moreover, local recurrences often show a higher grade than the primary tumor.<sup>13-15</sup>

Therefore, considering the possibility of malignancy—even if low in younger patients—and the high rate of local recurrences, a correct detection of a phyllodes tumor in a girl would lead to a subsequent clinical and surgical management totally different and

**Figure 2** Axial Views of <sup>18</sup>F-FDG PET/CT During Chemotherapy for Hodgkin Lymphoma. (A) CT, (B) PET, and (C) Fused PET/CT Images. A Focus of <sup>18</sup>F-FDG Avidity in the Right Breast Was the Only Pathological Finding in This Interim Examination. Focal Tracer Uptakes Seen Bilaterally in the Paravertebral Regions, Without CT Correlate, Were Consistent With Activated Brown Fat



Abbreviations: CT = computed tomography; <sup>18</sup>F-FDG = 18-fluorine-fluorodeoxyglucose; PET = positron emission tomography.

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obviously more aggressive than the one usually followed for fibroadenomas.<sup>4,12</sup>

Unfortunately, phyllodes tumors often have such an aspecific clinical presentation (dilated skin veins, blue discoloration of the skin, nipple retraction, fixation to the skin or the pectoralis muscle, a skin ulcer, pressure necrosis of the skin) that it is difficult to differentiate them from fibroadenomas, also because they ordinarily are unilateral and single lesions.<sup>4,12</sup> A clinical differential characteristic could be their usual appearance as masses with fast growth, increasing to an average diameter of 3 to 5 cm (sometimes they can even present as giant phyllodes tumors, with much bigger dimensions, more than 10 cm).<sup>12,16</sup>

Our young patient had a unique palpable lesion in the right breast with a maximum diameter of 5 cm. Its differential diagnosis was made difficult by the concomitant presence of an HL. Because the patient did not refer to any symptom, the pediatrician could perform the breast palpation only after the detection of the mass using <sup>18</sup>F-FDG PET/CT imaging. This case represents an example of good clinical practice; when <sup>18</sup>F-FDG PET/CT demonstrated a large uptake in the right mammary gland of the patient with diffuse HL and a breast US was requested as further additional investigation. Moreover, even though the US result was consistent with an HL metastasis in the breast, a further diagnostic examination (US-guided core biopsy) was made to exclude a primary tumor in the mammary gland. Actually, a secondary lesion from HL in the breast, although possible, would probably have been at least as rare as the finding of a phyllodes tumor in a young patient.<sup>17-20</sup> A phyllodes tumor, although large in dimension, might be asymptomatic and a pediatric patient might not notice or might underestimate the presence of a suspicious mass, as in our report. Hence, our case stresses also the importance in the daily clinical practice of an accurate breast examination in pediatric patients.

Interim PET/CT scan, performed after 2 cycles of chemotherapy, was extremely useful in our patient who carried 2 concomitant neoplasms. The only lesion that persisted was just the one in the right breast, and the others (really lymphomatous) showed complete response to treatment.

Besides, this case is a clear demonstration of how difficult the differential diagnosis of breast nodules can be, at a clinical level and using imaging. Although US plays an important role in the diagnostic flow chart of these tumors, further examinations are often necessary for the final diagnosis and exclude fibroadenomas.<sup>4,12,21,22</sup> In this case, performing an echo-guided core biopsy had been the correct choice, because it is the most accurate diagnostic examination for the detection of phyllodes tumors, second only to histology after surgery.<sup>4,12,23,24</sup>

Even though PET/CT imaging has been widely studied in lymphomas and in breast cancer, there is a lack of literature about the role of PET/CT in the diagnosis of phyllodes tumors, because of the rarity of this disease.<sup>25-28</sup> In 1996, Holle et al first showed an intense <sup>18</sup>F-FDG uptake in a rapidly growing phyllodes tumor.<sup>29</sup> Two years later, Bakheet and colleagues reported the case of a 22-year-old woman with an <sup>18</sup>F-FDG avid focus in the right breast corresponding to the local recurrence of a cystosarcoma phyllodes.<sup>30</sup>

Conversely, lots of recent studies have been conducted to identify imaging and histopathological markers able to differentiate phyllodes tumors from fibroadenomas and the benign cases from the borderline and the malignant ones, to correctly address clinical and surgical management of patients and find new treatment strategies.<sup>2,3,5,31,32</sup>

Further studies are warranted to investigate the ability of SUVmax (or, maybe, more accurate parameters such as metabolic unit volume and total lesion glycolysis) in differentiating benign, borderline, and malignant phyllodes lesions and the role of <sup>18</sup>F-FDG PET/CT in the prediction of their local recurrences or distance metastases. In any case, we should consider that benign neoplasms of the breast, such as fibroadenomas, sometimes can show a high <sup>18</sup>F-FDG avidity on PET/CT.<sup>33</sup>

Finally, our case clearly shows the role of PET/CT not only in the detection of phyllodes tumors, but also in the clinical management of patients, having been able to distinguish postsurgical changes from residual/early local recurrence of disease.

## Conclusion

We reported a rare case of phyllodes tumor of the breast in a young girl affected by HL. In the literature this is one of the few cases of breast phyllodes tumor detected with <sup>18</sup>F-FDG PET/CT and, to the best of our knowledge, the first reported in an adolescent. PET/CT proved to be a great tool in the diagnosis and management of such an uncommon neoplasm, because it helped in distinguishing primary phyllodes tumor from HL lesions. Further studies are necessary to evaluate if PET/CT with <sup>18</sup>F-FDG allows recognition of benign phyllodes lesions from borderline and malignant ones, and to predict phyllodes recurrences and distant metastases.

## Disclosure

The authors have stated that they have no conflicts of interest.

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