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Case Report

Head-to-head comparison of [^{18}F]-fluorodeoxyglucose and [^{18}F]-fluorocholine positron emission tomography/computed tomography in three patients with rare gestational trophoblastic neoplasms: A case series

ABSTRACT

We report the efficacy of dual positron emission tomography/computed tomography (PET/CT) imaging with [^{18}F]-2'-fluoro-2'-deoxy-D-glucose ([^{18}F]-FDG) and [^{18}F]-fluorocholine ([^{18}F]-FCH) in patients with gestational trophoblastic neoplasia (GTN) for primary diagnosis and staging of this rare pregnancy-related disorder. Whole-body PET/CT with [^{18}F]-FDG and [^{18}F]-FCH was performed in three patients with GTN in 2 consecutive days. Each detectable lesion was characterized by visual and quantitative analyses. As compared to CT alone, PET/CT with [^{18}F]-FDG and [^{18}F]-FCH PET/CT revealed more hypermetabolic metastatic lesions in the body, but not in the brain. The standard uptake value of [^{18}F]-FDG was generally higher than [^{18}F]-FCH in all detectable tumor lesions. In conclusion, both [^{18}F]-FDG and [^{18}F]-FCH PET/CT can be used for diagnosis and staging for GTN, based on their sensitivity for small extracerebral metastatic lesions. Additional studies are warranted to determine whether the PET/CT imaging with [^{18}F]-FDG and [^{18}F]-FCH can serve as a biomarker of GTN aggressiveness, for prediction of treatment response.

Keywords: [^{18}F]-2'-fluoro-2'-deoxy-D-glucose, [^{18}F]-fluorocholine, choriocarcinoma, gestational trophoblastic neoplasia, positron emission tomography/computed tomography

INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is a rare pregnancy-related neoplasm. The incidence of GTN in South East Asia, including Thailand, is 3–16 times higher than in Western countries.[1] Metastases have been reported in 19% of GTN, most commonly to the lung, followed by brain and liver.[2]

Molecular imaging can be helpful in diagnosis and staging of GTN, by more accurately determining the sites and number of metastatic lesions, monitoring treatment responses, and predicting the resistance to chemotherapy. [^{18}F]-2'-fluoro-2'-deoxy-D-glucose ([^{18}F]-FDG) positron emission tomography/computed tomography (PET/CT) can localize glycolytically active lesions; however, false interpretations, indeterminate lesions, and limitations in hyperglycemic patients have been reported.[3,4] Many cancers have also increased choline metabolism associated with

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increased cell membrane turnover.[5] Increased choline uptake in GTN cells is mediated by overexpression of high- and low-affinity choline transporters.[6,7] Choline PET imaging has been used in other gynecologic malignancies,[8] but not in GTN. We present the results of PET/CT studies with [18F]-FDG and [18F]-fluorocholine (FCH) in three patients with different types of GTN in comparison with histopathological findings, treatment responses, and the overall outcome.

CASE REPORTS

This study was approved by the institutional review board (COA No. Si 744/2017) and all subjects signed informed consent form. PET/CT imaging studies were conducted in three patients, who had fulfilled the criteria for the diagnosis of GTN. Both [18F]-FDG and [18F]-FCH PET/CT were manufactured in accordance with CGMP at our hospital, using a fully automated radiosynthesis system (Sumitomo Heavy Industries, Japan). Imaging studies were performed using Discovery STE PET/CT scanner (GE Healthcare, Milwaukee, WI, USA). First, static PET/CT images from skull vertex to the mid-thigh were obtained at 60 min after intravenous administration of [18F]-FDG (5.18–7.4 MBq/kgBW). On the next day, dynamic PET/CT images of pelvic region were obtained during 0–10 min postadministration of [18F]-FCH (370 MBq/patient), followed by static whole-body PET/CT imaging, starting at 60 min postadministration. Each lesion was characterized by visual and quantitative analyses, and the levels of radioactivity accumulation were expressed as standard uptake values.

Case 1

A 47-year-old woman was diagnosed with molar pregnancy postcurettage with initial serum βHCG of 300,000 mIU/ml, which decreased to 10,000 mIU/ml after the first cycle of chemotherapy. However, the symptoms of vaginal bleeding persisted, with persistently high serum βHCG. Preoperative PET/CT with [18F]-FDG and [18F]-FCH both demonstrated mild hypermetabolism in the peripheral rim of the primary tumor [Figure 1 and Table 1].

The patient underwent a total hysterectomy with bilateral salpingo-oophorectomy. Pathological examination confirmed the invasive hydatidiform mole with invasion to myometrium and left adnexal vessels, resulted in GTN Stage II, Score 6. Serum βHCG fell to normal level after eight cycles of chemotherapy. The patient is still free from the disease clinically and biochemically for 18 months after chemotherapy withdrawal.

Case 2

A 52-year-old woman, who was diagnosed with an intermediate trophoblastic tumor and had undergone a total hysterectomy with bilateral salpingo-oophorectomy

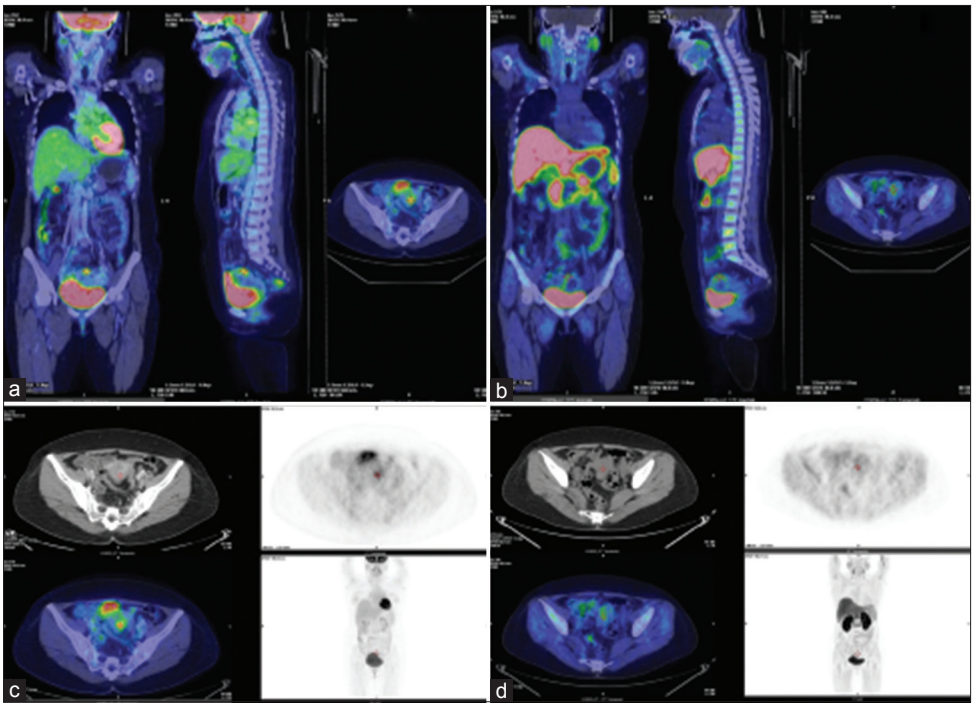

Figure 1: [18F]-2'-fluoro-2'-deoxy-D-glucose positron emission tomography/computed tomography images of a 47-year-old woman with gestational trophoblastic neoplasia for preoperative staging found a small hypermetabolic lesion with modest enhancement on computed tomographyin the upper endometrial wall, but without the evidence of active metastasis. The [18F]-2'-fluoro-2'-deoxy-D-glucose positron emission tomography/computed tomography study (a and c) revealed similar findings as [18F]-fluorocholine (b and d), but the magnitude of [18F]-fluorocholine accumulation was much lower than that of [18F]-2'-fluoro-2'-deoxy-D-glucose

7 years ago, presented with recurrent bleeding. She underwent exploratory laparotomy with tumor resection and postoperative chemotherapy but had to withdraw after the fourth cycle due to renal impairment. The serum βHCG was continuously rising: from 3.36 mIU/ml to 28.31 mIU/ml over 9 months postsurgery. Contrast-enhanced CT demonstrated tumor recurrence in the mid-left side of the vaginal stump and several pulmonary nodules, which showed progression in the follow-up CT study.

Table 1: Comparison of quantitative analysis results for each lesion detected by both positron emission tomography/computed tomography studies in three patients

Case/lesion	Size (cm)	Lesion (background)			FDG/FCH ratio	
		FDG	FCH			
		SUV_{60min}	SUV_{10min}	SUV_{60min}	Early	Delay
1 primary	8.4×6.7×4.5	6.2 (1.1)	3.4 (2.0)	2.5 (2.5)	9.9	5.6
Metastasis	No	No	No	No	No	No
2 primary	6.4×5.5×3.5	1.3 (0.7)	1.3 (1.4)	1.4 (1.8)	1.7	0.7
Metastasis 1	1.9×2.0×2.0	1.9 (1.0)	NA	1.5 (0.8)	-	3.6
Metastasis 2	2.3×2.1×1.7	2.0 (0.9)	NA	1.8 (1.0)	-	4.0
Metastasis 3	2.6×2.4×1.3	2.2 (1.2)	NA	1.7 (1.6)	-	1.9
Metastasis 4	2.5×1.6×1.8	2.5 (1.1)	NA	1.7 (1.5)	-	2.5
3 primary	No	No	No	No	No	No
Metastasis	2.5×1.4×1.0	3.1 (1.0)	NA	2.5 (1.6)	-	4.8

SUV reported in this table were maximum values within the ROI. The SUV in the adjacent muscle region was used as background and for further calculation of lesion to background ratio. FCH: Fluorocholine; SUV: Standard uptake values; FDG: 2′-fluoro-2′-deoxy-D-glucose; NA: Not available; ROI: Region of interest

The patient refused radiation therapy, so preoperative chemotherapy was initiated but then discontinued due to complications. Then, a laparoscopic examination and adhesion lysis were performed, revealing a 2 cm × 3 cm mass located on the left side above the vaginal stump, adherent to the left ureter. Because serum βHCG levels continued to rise up to 1110 mIU/ml and the patient developed severe headaches, CT scan of the brain was performed and revealed a small ill-defined hyperdense lesion in the left posterior aspect of the parietal lobe with perifocal edema but no contrast enhancement which could not exclude a metastasis-associated hemorrhage. Both [18F]-FDG and [18F]-FCH PET/CT studies obtained 2 months later demonstrated low uptake of both tracers in the primary tumor and in the brain lesion. In contrast, all metastatic lesions in the lungs were hypermetabolic, especially with [18F]-FDG [Figures 2, 3 and Table 1].

The patient was diagnosed with GTN Stage III, Score 11. Consistent with this bad prognosis, the patient's serum βHCG level continued to rise up to 1765 mIU/ml during 16 months after PET/CT studies, even during aggressive chemotherapy. The fate of this patient at present is unknown because contact with this patient was lost.

Case 3

A 36-year-old woman was diagnosed with choriocarcinoma with lung metastasis and 3-year history of seizures of unknown etiology. The patient was initially treated with chemotherapy and effective anti-epileptic therapy. Patient's serum βHCG

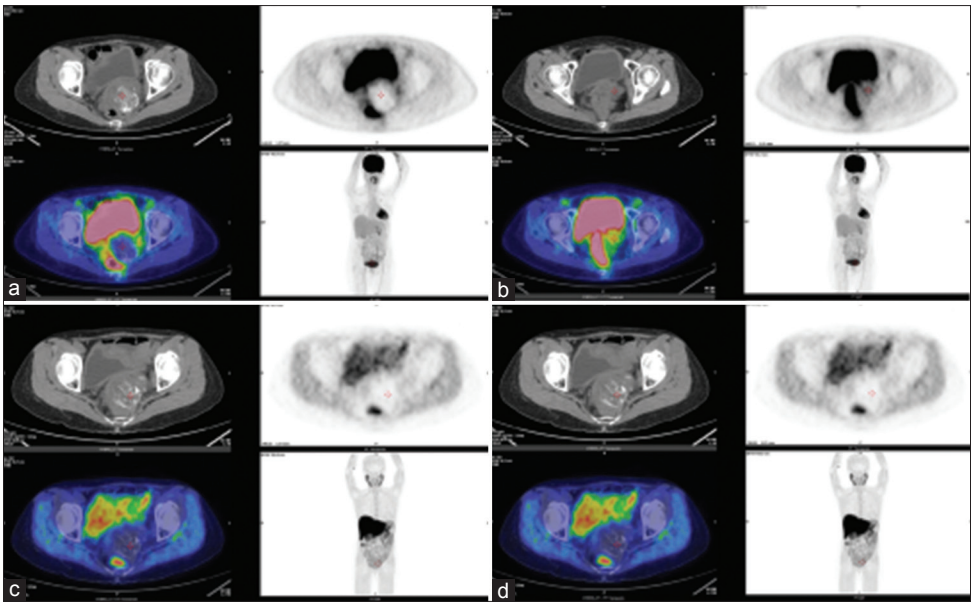

Figure 2: Whole-body positron emission tomography/computed tomography images of a 52-year-old woman with recurrent gestational trophoblastic neoplasia, posttotal hysterectomy with bilateral salpingo-oophorectomy. No hypermetabolic lesions were detectable at the residual calcified mass after chemotherapy in either [18F]-2′-fluoro-2′-deoxy-D-glucose positron emission tomography/computed tomography (a and b) or [18F]-fluorocholine positron emission tomography/computed tomography (c and d). Contrast material was not used due to severely impaired renal function

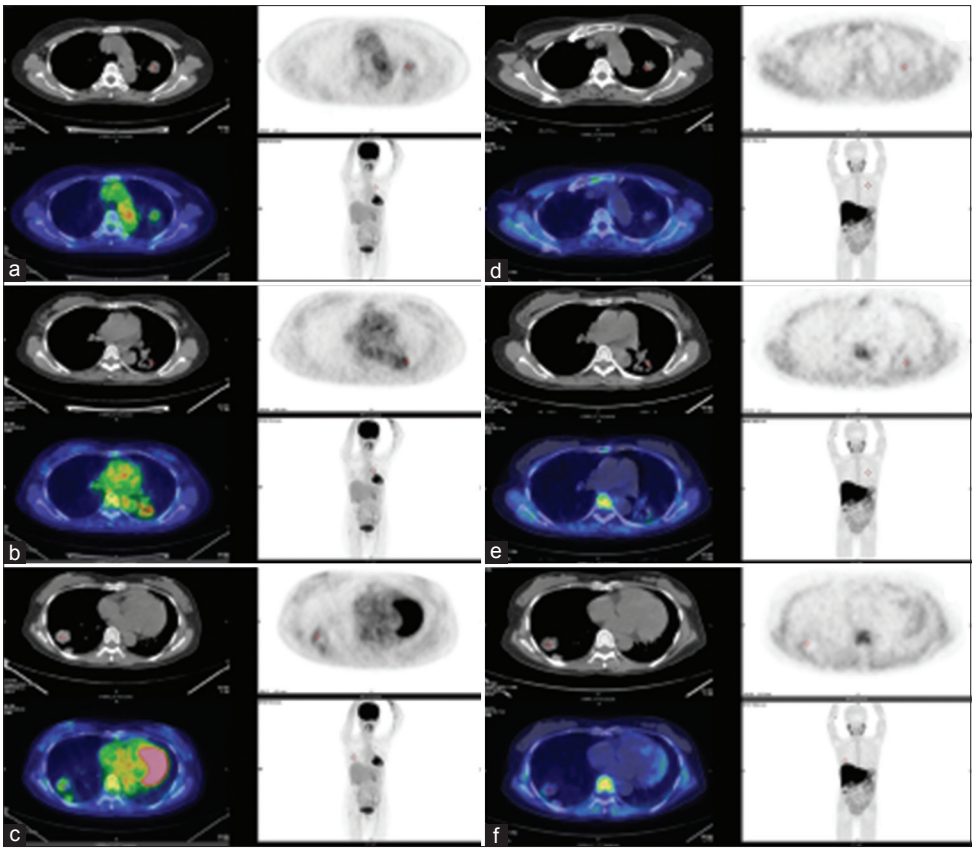

Figure 3: Whole-body [18F]-2′-fluoro-2′-deoxy-D-glucose positron emission tomography/computed tomography study (without contrast) in the same patient (Case 2) revealed multiple hypermetabolic pulmonary nodules in both lungs, suggestive of pulmonary metastases (a-c), which on the [18F]-fluorocholine positron emission tomography/noncontrast computed tomography study showed less uptake intensity in the corresponding lesions (d-f)

level had risen from 0.88 to 81.66 mIU/ml during 5 months of chemotherapy. The patient underwent total hysterectomy and the residual tumor was not detectable. The serum βHCG level kept rising during the 8 months of postsurgical chemotherapy. Diagnostic CT scan revealed a few new pulmonary nodules (0.2–0.3 cm in size) without an evidence of local recurrence. [18F]-FDG and [18F]-FCH PET/CT studies revealed a hypermetabolic pulmonary nodule in the left lower lobe, suggestive of pulmonary metastasis [Figure 4 and Table 1]. The patient was diagnosed with GTN Stage III, Score 14. Two months after the PET/CT studies, the patient suddenly developed a disturbance of consciousness, left hemiparesis, and symptoms of left oculomotor nerve palsy. An emergency CT scan of the brain revealed an acute subdural hemorrhage originating from the bleeding metastatic tumor lesion in the left temporal lobe and the presence of several other brain metastatic lesions. Patient's neurological symptoms improved after tumor excision, followed by palliative whole-brain 3D conformal radiation therapy and chemotherapy, but high levels of βHCG in the serum still persisted. The patient died 3 months later due to progression of brain metastasis, acute decompensation of chronic kidney disease, pancytopenia, and urinary tract and pulmonary tract infection-induced sepsis.

DISCUSSION

This case series has demonstrated the potential utility of PET/CT imaging with [18F]-FDG and [18F]-FCH in GTN. To the best of our knowledge, this is the first report describing the results of PET/CT with [18F]-FCH in this particular tumor type. The uptake of [18F]-FDG was higher than [18F]-FCH in all detectable lesions. In the first patient, PET/CT studies performed before the surgical resection demonstrated significant intratumoral heterogeneity, with only a small region of increased glucose and choline metabolism within the primary tumor lesion, but not in other active disease sites, which were associated with good treatment response. In the other two cases, in which primary tumors were already treated, both PET/CT studies confirmed the absence of active loco-regional disease. The most common site of demonstrable metastatic disease in these patients was in the lungs, with higher uptake of [18F]-FDG. Both PET/CT studies were more sensitive in detecting tiny subpleural metastatic nodules as compared to CT studies. However, due to lower resolution of PET and low-dose CT used in hybrid PET/CT, very small metastatic GTN lesions may demonstrate false-negative results.

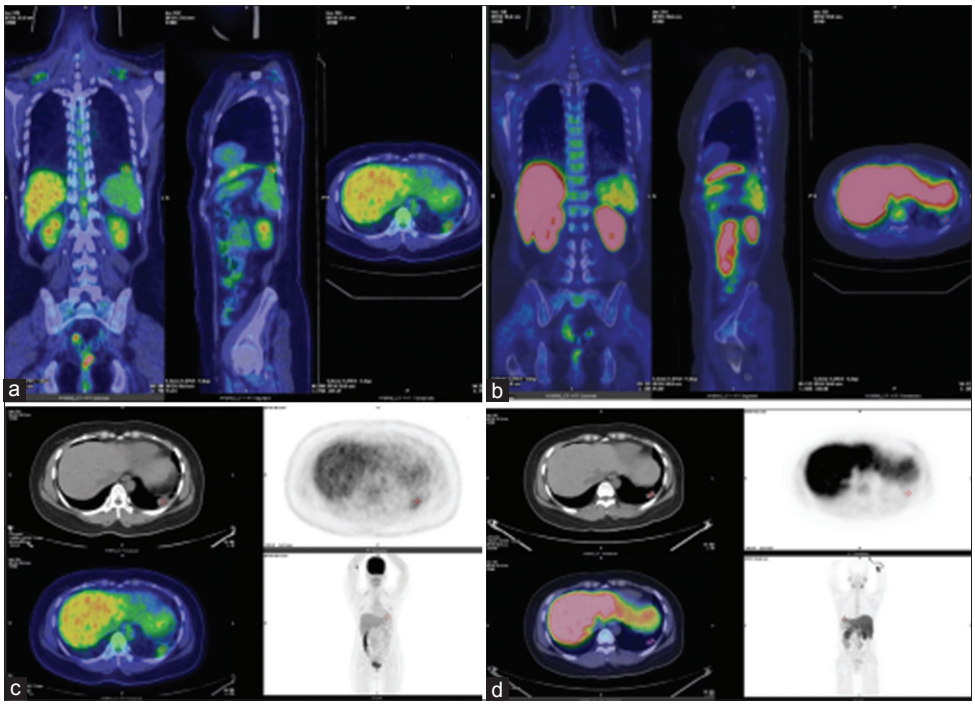

Figure 4: [18F]-2'-fluoro-2'-deoxy-D-glucose positron emission tomography/computed tomography images of a 36-year-old patient with choriocarcinoma and lung metastases, acquired 5 months postchemotherapy, revealed a hypermetabolic pulmonary nodule located in the left lower lobe, suggestive of pulmonary metastasis (a and c), which on the [18F]-fluorocholine positron emission tomography/computed tomography study showed similar but less uptake intensity (b and d). The surgical bed and regions elsewhere were unremarkable

The second most common metastatic site in these patients was the brain. We expected that [18F]-FCH will have higher specificity than [18F]-FDG for detection of brain metastasis. However, both studies failed to detect the intracranial lesion in one patient with an indeterminate lesion seen in a preceding CT study (Case 2). This patient is still free from neurological symptom during 18 months of follow-up, so brain metastases might possibly be ruled out. However, in another patient, who exhibited rapidly worsening clinical symptoms and had imaging findings of hemorrhagic brain metastasis, both PET/CT studies also cannot be used for detection of brain metastases of GTN or for prognosis. Rapid progression of brain metastasis of choriocarcinoma has been reported previously.[9] Therefore, screening and close monitoring of potential metastatic GTN lesions in the brain using MRI are still recommended in high-risk patients (e.g., extremely high serum βHCG level), even if the [18F]-FDG and [18F]-FCH studies show negative results.

None of the patients in our series had a hepatic metastasis. Therefore, the roles of [18F]-FDG and/or [18F]-FCH in this situation should be investigated. Furthermore, all these patients had undergone treatment before the PET/CT studies; thus, untreated patients may produce different imaging results.

One limitation of [18F]-FCH is its significant bladder activity. In contrast, [11C]-choline is eliminated predominantly by hepatobiliary excretion and may have an advantage over the [18F]-FCH for detection of lesions in the pelvis. However, the short half-life of [11C] limits its wide use in routine clinical studies. We used early dynamic images of pelvic region followed by delayed whole-body imaging after voiding, which showed no significant bladder activity that could complicate the detection of primary tumors or postsurgical recurrence. Other interventions, such as retained urinary catheter or diuretic administration together with volume loading, are not generally acceptable because these procedures cause unnecessary discomfort and also increase the risk of infection.

CONCLUSION

PET/CT studies, with either [18F]-FDG or [18F]-FCH, could play an important role in the accurate staging and scoring of GTN and may improve the understanding of roles that glucose and choline metabolic pathways play in aggressiveness and treatment response. Even though, in our series, the [18F]-FCH uptake was lower than [18F]-FDG, it may be an alternative option in patients with potentially limited efficacy of [18F]-FDG. Rapid progression of brain metastasis may not be predictable by the baseline PET/CT studies; thus, additional neuroimaging studies with MRI are recommended.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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