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Malignant Lymphoma Imaged by ^{18}F-Fluoro-Choline PET-CT in a Patient with Prostate Cancer: a Case Report and Review of Literature

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Abstract

PET-Choline imaging has gained a pivotal role in the assessment of patients with biochemical relapse of prostate cancer. Its use is more limited in other pathologies like brain tumours and hepatocellular carcinoma. Nevertheless, albeit infrequent, incidental detection of a metachronous tumor has been reported in patients with suspected recurrence of prostate cancer.

Herein we report the case of a 70-years-old man with prostate cancer treated with permanent brachytherapy, presenting a biochemical recurrence, bone pain and multiple lesions on bone scan. Fluorine 18-Choline PET-CT revealed a large involvement of the right hemipelvis, pelvic floor, lumbar and thoracic spine with invasion of surrounding soft tissues.

Because lytic aspect at CT of the bone lesions and PSA values lower than expected in bone metastases, FNAB and biopsies were performed and revealed a Diffuse Large B Cell Lymphoma. Complete remission and PSA normalization was achieved after immuno-chemotherapy.

Radioactive Choline shares its mechanism of uptake with a large variety of cancers and benign diseases.In addition the incidence of secondary primary malignancy in prostate cancer has been reported recently as 14%, the pairing with non Hodgkin's Lymphoma being less frequent, the 4.5% of all synchronous and metachronous malignancies observed. In this paper we reviewed and discussed the data published in literature regarding accumulation of labelled choline in lymphoproliferative diseases. Albeit the scarce number of cases recorded, the radiopharmaceutical shows a good affinity for this pathology. Therefore in the presence of Choline accumulation sites in patients with prostate cancer different from the typical spread pattern or accompanying not characteristic features, one must be aware of possible pitfalls, either in false positive results in benign conditions or in the attribution of the detected lesions to a second primary malignancy.

Keywords: ^{18}F-fluorocholine, PET-CT, lymphoma, prostate adenocarcinoma, PSA.

Introduction

Choline is a major component of cell membranes and a marker of increased cellular metabolism, typical of neoplastic tissues. PET-CT with choline, labelled with ^{11}C (CCH) or ^{18}F (FCH), is commonly employed in patients with prostate cancer (PCa), especially in the event of biochemical recurrence.The test accuracy is higher with PSA value (> 2 ng/mL) rapidly rising (Doubling Time < 6 months) and lower

in some body areas ororgans where a physiological uptake can mask possible metastatic foci. In recent years several papers reported the potential use of this tracer in other histotypes and in some body areas as for instance inthe brain [1-5],where background is virtually absent and high Target-to-Non-Target (TNT) ratios can be achieved.

Although these studies did not demonstrate entirely clear advantages in comparison with other PET tracers in terms of accuracy, it is clear that many other cancer types and some benign conditions, characterized by enhanced choline metabolism, may cause misinterpretation of the PET results either in terms of specificity or attribution of the detected lesions to a second primary malignancy [6].

Nevertheless, there are relatively few reports regarding Choline PET detection of lymphoproliferative diseases.

Case Report

A 70-year-old man with prostate hyperplasia (volume close to 50 mL) and PSA 14 ng/mL, underwent fine-needle aspiration biopsy (FNAB) which demonstrated the presence of a single focus of PCa in the middle lobo, Gleason 6 (3+3), occupying less than 5% of the sample, negative staining with MAb anti-cytokeratin 34betaE12. Pelvic CT and MRI confirmed the absence of extra prostatic involvement (T1c N0 M0). A FCH PET-CT scan was performed to investigate the origin of elevated PSA value. Early scan showed a diffuse prostate uptake with near complete wash-out in the late scan except for a minimal residual activity in the right side, it was concluded for inflammatory changes responsible for PSA elevation. Therefore the patient was treated with transrectal ultrasound-guided permanent brachytherapy (125I seeds, 145 Gy).

Sixteen months later, osseous metastases were suspected because of bone pain and increased PSA values (4.62 ng/mL). Bone scan with ^{99m}Tc-diphosphonate showed multiple lesions involving the right hemipelvis and spine. Because of rapidly increasing PSA levels (doubling time 2.86 months), three weeks later a ^{18}F-fluorocholine (FCH)PET-CT was performed. Early and late scans showed a large area of pathological uptake (SUVmax7) involving

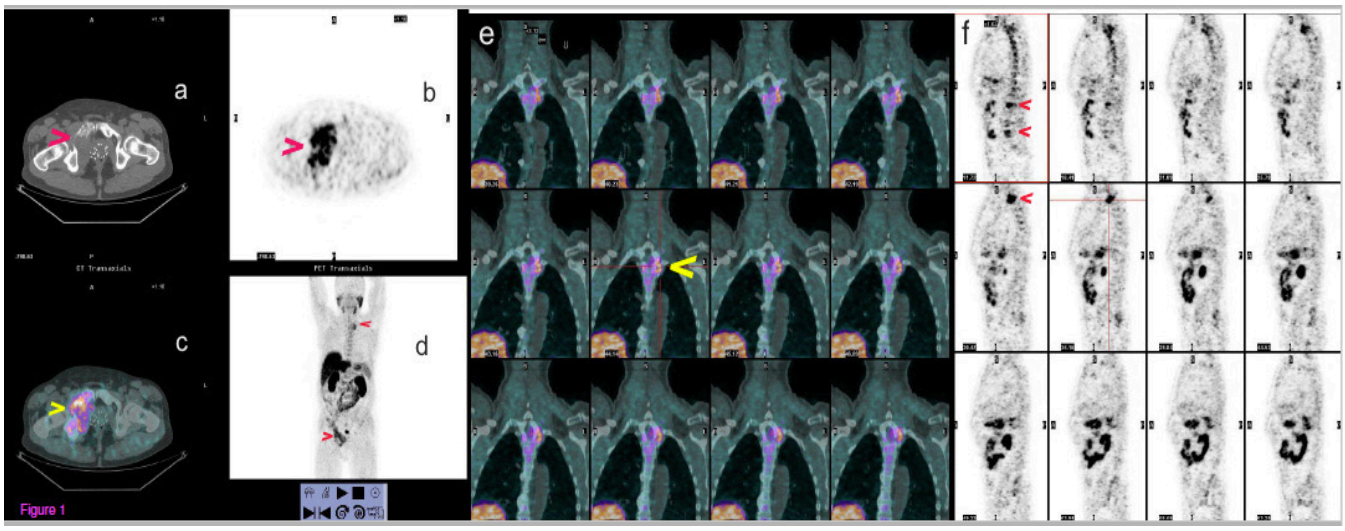

Fig. 1- PET-CT scan obtained 1 hour after FCH injection. **a**: CT transverse section showing extensive lytic involvement of the right hemipelvis (arrowhead). **b**: corresponding PET slice, showing an intense FCH accumulation in the bone and surrounding soft tissue of the pelvic floor. **c**: PET-CT fused image, note the absence of FCH accumulation in the right prostatic bed (125I seeds implanted).**d**: MIP (maximum intensity projection) showing FCH accumulation in the right hemipelvis and thoracic spine. Physiological uptake in the salivary glands, liver and gut.**e**: fused coronal PET-CT views of the thoracic spine, vertebral and perivertebral FCH accumulation (arrowhead).**f**: sagittal PET views of the spine showing accumulation in the thoracic and lumbar spine (arrowheads).

bone of the right hemipelvis and infiltrating the soft tissues of the pelvic floor on the right side. In addition, pathological uptake had infiltrated the adjacent soft tissues in the thoracic (T1-T3) and lumbar spine (L1-L2). Corresponding CT images revealed a lytic appearance with moth-eaten aspects [Figure 1].

Contrast enhanced CT and MRI confirmed the spine lesions with intracanalar and perivertebral invasion, involvement of the bone and soft tissues of the right hemipelvis.

Pelvic FNAB,performed as CT images of bone lesions were not characteristic of PCa,revealed highly malignant Diffuse Large B Cell Lymphoma (DLBCL), LCA+, CD20+, bcl2+, bcl6+, CD10+/-, Mum 1-, Mib1/ki67: 60%. Thereafter, the patient underwent surgery for thoracic spine stabilization and decompression. Biopsy confirmed the diagnosis of DLBCL.

A complete remission was achieved after 6 cycles of R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone). During the course of chemotherapy the patient was treated with dutasteride and serum PSA values returned within the normal range (0.38 ng/mL after the last course).

Discussion

Bone pain, rapidly increasing PSA and bone scan images were consistent with bone metastases of PCa.

Label	Pts n°	Site (foci n°)	Method of verification	Final diagnosis	AA,year [ref]
^{18}F	1	Nodes, spleen	histology	Hodgkin Lymphoma	Goineau, 2015 [8]
^{11}C	1	Brain	histology	NK-cell Lymphoma	Li, 2015 [9]
^{11}C	1	Ureter	histology	malignant lymphoma NOS	Sassa, 2014 [10]
^{11}C	1	Nodes	histology	DLBCL	Garzon, 2014 [11]
^{18}F	1	Thyroid	cytology (FNAB)	DLBCL	Eccles,2013 [12]
^{18}F	1	Nodes	histology	Low grade follicular lymphoma	Schillaci, 2010[13]
^{11}C	2	Brain	n/a	Lymphoma NOS (1false neg)	Huang, 2008 [2]
^{11}C	5	Mediastinum	histology	Lymphoma NOS	Peng, 2007 [14]
^{11}C	n/a	Brain(1) Head & Neck (6) Soft tissue (2)	histology	Malignant Lymphoma NOS, Active lymphoid hyperplasia (3 false positives)	Tian, 2004 [5]
^{11}C	6	Head & Neck (7)	histology	5 malignant lymphoma NOS, 1 low grade lymphoma, 1 lymphoid hyperplasia (false pos)	Khan, 2004 [15]
^{11}C	2	Brain	n/a	DLBCL, metastatic lymphoma NOS	Utriainen, 2003 [3]
^{11}C	1	Brain	histology	Malignant Lymphoma NOS	Shinoura, 1997 [1]

(NOS: not otherwise specified; DLBCL: Diffuse Large B Cell Lymphoma; n/a: not available)

Table-1 Summary of available data in the literature of lymphoma localizations imaged by CH-PET.

Although FCH PET-CT confirmed the initial diagnosis of PCa with soft tissues and bone involvement, the relatively low value of PSA (4.62 ng/mL) and the CT lytic aspect of bone lesions were less consistent with this hypothesis. In fact, results of biopsy pointed to a highly malignant lymphoproliferative disease. FCH PET correctly depicted the body involvement, except the invasion of the right prostatic bed where no significant choline uptake was detected.

Choline is a fundamental component of phospholipids of the cell membrane, increased cellular metabolism as in the neoplastic tissues leads to an increased uptake of this substrate. Therefore is not surprising that a large variety of cancers other than PCa can accumulate Choline at a high degree [1],allowing external detection of a large series of histotypes including head & neck, brain, lung, gynaecological, urinary tract, muskuloskeletal and liver neoplasm [7].

There are relatively few reports regarding Choline-PET detection of lymphoproliferative diseases in the literature [Table 1] [1-3, 5, 8-15].

In the majority of cases, mainly case reports, information about the histological variant and the proliferation index (ki-67) is lacking. In this regard, Utriainen[3]found a higher SUV in lymphomas than in other brain tumours in his series and a significant, albeit non predictive, relationship between Patlak Ki accumulation rate and ki-67. Higher SUV has been reported in mediastinal lymphoma lesions, however not significantly different in comparison with benign lesions due to the wide distribution of values[14].

Although Tian[5] claims a better specificity of CH compared to FDG for some body areas, his series reveals a wide SUV overlapping between malignant lymphomas and active lymphoid hyperplasia. A dual point study, i.e. comparison of SUV in early and late scans, is better able to discriminate between benign and malignant lesions with an improved specificity [2, 14] .Choline-PET sensitivity seems quite high, even if a brain localization [2] and the right lobe prostatic involvement here described were false negatives.

Another point worth of note is that PSA values normalized after starting dutasteride treatment and during the course of R-CHOP immuno-chemotherapy. Benign prostatic hyperplasia is a known confounding factor of PCa marker, however the rapid PSA rise was highly suggestive of a biochemical recurrence. In addition, antitumor properties of 5-alpha-reductase-inhibitor monotherapy have never been demonstrated in patients. One hypothesis could be that very small foci of recurrent prostate cancer, responding to R-CHOP regimen, were present but were not revealed due to the detection limits of CH-PET. Another possible explanation is that raised PSA levels may be due to the presence of NHL secreting neoplastic cells, as reported for positive PSA immunostaining in the literature[16].

Conclusion

In conclusion, Choline-PET is becoming widely accepted in the early detection of PCa recurrence with a significant impact on prognosis and therapy. However, its uptake is shared with numerous malignant neoplasms as well as benign lesions. Therefore, clinicians must be aware of possible pitfalls in interpreting results if it accumulates in sites unrelated to the typical spreading pattern of PCa, for instance in mediastinal nodes where reactive/inflammatory conditions are more likely[17, 18], or in unusual accompanying findings, as in the present case, where the lytic aspect of bone metastases on CT is less likely to occur. Therefore, another metachronous tumour must be taken into account, even in the event of rapidly rising PSA. In a recent epidemiological analysis of a Caucasian population, Levi [19]reported a 14% incidence of either synchronous or metachronous second primary malignancies in 441 male subjects with first primary PCa, 17 cases of which (incidence 3.8%) were metachronous NHL. A lower incidence (1.3%) of a secondary solid malignancy has been reported with FCH-PET [20] in metastatic PCa patients. However the true incidence could be underestimated owing to the reduced accuracy of CH in detecting pathological accumulation in organs with a high physiological uptake, like liver, gut and kidney, accounting for a relevant proportion of cancer pairing.

References

1. Shinoura N, Nishijima M, Hara T, Haisa T, Yamamoto H, Fujii K, Mitsui I, Kosaka N, Kondo T, Hara T:Brain tumors: detection with C-11 choline PET. Radiology 1997;202:497-503.
2. Huang Z, Zuo C, Guan Y, Zhang Z, Liu P, Xue F, Lin X. Misdiagnoses of11C-choline combined with18F-FDG PET imaging in brain tumours. Nucl Med Commun 2008;29:354-358.
3. Utriainen M, Komu M, Vuorinen V, Lehikoinen P, Sonninen P, Kurki T, Utriainen T, Roivainen A,Kalimo H, Minn H. Evaluation of brain tumor metabolism with [11C]choline PET and 1H-MRS. JNeurooncol 2003;62:329-338.
4. Basu S, Alavi A: Molecular imaging (PET) of brain tumors. Neuroimaging Clin N Am 2009,19:625-646.
5. Tian M, Zhang H, Oriuchi N, Higuchi T, Endo K: Comparison of11C-choline PET and FDG PET forthe differential diagnosis of malignant tumors. Eur J Nucl Med Mol Imaging 2004;31:1064-1072.
6. Leung, K (2011): [11C]Choline. Molecular Imaging and Contrast Agent Database (MICAD).http://www.ncbi.nlm.nih.gov/books/NBK23549/.
7. Treglia G, Giovannini E, Di Franco D, Calcagni ML, Rufini V, Picchio M, Giordano A. The role ofpositron emission tomography using carbon-11 and fluorine-18 choline in tumors other than prostatecancer: a systematic review. Ann Nucl Med 2012;26:451-461.
8. Goineau, A, Colombié M, ,Rousseau C, Sadot-Lebouvier S, Supiot S. Incidental detection of a Hodgkin lymphoma on 18F-choline PET/CT and comparison with 18F-FDG in a patient with prostate cancer. ClinNucl Med 2015;40: 670–671
9. Li LF, Taw BB, Pu JK, Hwang GY, Lui WM, Leung GK.Primary Central Nervous System Natural Killer Cell Lymphoma in a Chinese Woman with Atypical (11)C-Choline Positron Emission Tomography and Magnetic Resonance Spectrometry Findings. World Neurosurg2015 ;84: 1176.e5-.e9.
10. Sassa N, Kato K, Abe S, Iwano S, Ito S, Ikeda M, Shimamoto K, Yamamoto S, Yamamoto T, Gotoh M,Naganawa S. Evaluation of (11) C-choline PET/CT for primary diagnosis and staging of urothelialcarcinoma of the upper urinary tract: a pilot study. Eur J Nucl Med Mol Imaging 2014;41:2232-2241.
11. Garzon JG, Bassa P, Moragas M, Soler M, Riera E. Incidental diagnosis of diffuse large B-celllymphoma by11C-choline PET/CT in a patient with biochemical recurrence of prostate cancer. ClinNucl Med 2014;39:742-743.
12. Eccles A, ChallapalliA, Khan S, Barwick T, Mangar S. Thyroid lymphoma incidentally detected by18F-fluorocholine (FCH) PET/CT. ClinNucl Med 2013;38:755-757.
13. Schillaci O, Calabria F, Tavolozza M, Cicciò C, Carlani M, Caracciolo CR, Danieli R, OrlacchioA,Simonetti G.18F-choline PET/CT physiological distribution and pitfalls in image interpretation:experience in 80 patients with prostate cancer. Nucl Med Commun 2010;31:39-45.
14. Peng ZM, Liu Q, Liu QW, Yao SZ, Meng L, Liu Q, Chen JH. The value of dual time point11C-cholinePET-CT in differentiating malignant from benign lesion of mediastinum. Zhonghua Yi XueZaZhi 2007;87:3317-3320.
15. Khan N, Oriuchi N, Ninomiya H, Higuchi T, Kamada H, Endo K. Positron emission tomographicimaging with11C-choline in differential diagnosis of head and neck tumors: comparison with18 F-FDGPET. Ann Nucl Med 2004;18:409-17.
16. OosterheertJJ, Budel LM, Vos P, Wittebol S. High levels of serum prostate-specific antigen due toPSA producing follicular non-Hodgkin's lymphoma. Eur J Haematol 2007;79:155-158.
17. Liu Q, Peng ZM, Liu QW, Yao SZ, Zhang L, Meng L, Chen JH. The role of 11 C-choline positron emission tomography-computed tomography and videomediastinoscopy in the evaluation of diseases of middle mediastinum. Chin Med J 2006;119:634-639.
18. Rietbergen DD, van der Hiel B, Vogel W, Stokkel MP. Mediastinal lymph node uptake in patientswith prostate carcinoma on F18-choline PET/CT. Nucl Med Commun 2011;32:1143-1147.

19. Levi F, Randimbison L, Rafael BM, Manuela MC, Vecchia CL. Second primary cancers in the Vaudand Neuchâtel Cancer Registries. Eur J Cancer Prev2015;24:150-154.
20. García JR, Ponce A, Canales M, Ayuso J, Moragas M, Soler M. Detection of second tumors in11CcholinePET/CT studies performed due to biochemical recurrence of prostate cancer. Rev Esp MedNuclImagenMol 2014;33:28-31.