Unusual diffuse liver ^{18}F-FDG uptake in melanoma patient treated by ipilimumab

Muteganya Raoul[1] **MD,**
Karfis Ioannis[1] **MD PhD,**
Artigas Carlos[1] **MD,**
Garcia Camilo[1] **MD,**
Francesco Feoli[2] **MD,**
Kerger Joseph[3] **MD,**
Flamen Patrick[1] **MD PhD**

1.Nuclear Medicine Department and Metabolic Therapies
2.Anatomo-Pathology Department
3.Oncologic Department, Jules Bordet Institute, Brussels, Belgium

Keywords: Ipilimumab -Induced hepatotoxicity -Melanoma -^{18}F-FDG PET/CT

Corresponding author:
Raoul Muteganya MD,
Nuclear Medicine Department and Metabolic Therapies,
Jules Bordet Institute.
121 Boulevard de Warteloo,
1000 Brussels, Belgium
Raoul.Muteganya@bordet.be

Received:
27 March 2017
Accepted revised:
3 May 2017

Abstract
We present herein a case of unusual ^{18}F-FDG PET-CT diffuse hypermetabolic liver uptake in melanoma patient treated by ipilimumab.

Hell J Nucl Med 2017; 20(2): 179-181 *Epub ahead of print: 12 July 2017* *Published online: 8 August 2017*

Introduction

Metastatic liver infiltration should be considered in case of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) diffuse and intense liver uptake in melanoma patients previously treated with ipilimumab (a cytotoxic T-lymphocyte antigen-4 (CTLA-4) blocking antibody). We report on a case of a 66 years old man diagnosed with melanoma of the right arm, treated with ipilimumab presenting with altered liver tests. Liver ultrasonography showed an heterogeneous hepatic parenchyma without focal lesions and no sign of obstruction. An ^{18}F-FDG PET/CT scan showed an unusual pattern with diffuse hypermetabolic liver uptake. Anatomopathology confirmed a diffuse metastatic infiltration of the liver. This pattern of ^{18}FDG uptake is the first reported to the best of our knowledge.

Case Report

We report on a case of a 66 years old man diagnosed in 2007 with melanoma of the right arm (0.8mm Breslow depth, Clark level III and no ulceration). He initially underwent surgery with tumor free margins. No search of sentinel lymph node was made. Six years after the initial diagnosis, axillary lymph node recurrence occurred. The patient received vemurafenib (a BRAF inhibitor therapy) and dacarbazine as first and second line treatment, respectively. Although the BRAF mutation was present, unfortunately, no metabolic response was observed with vemurafenib. A third line treatment with ipilimumab (a cytotoxic T-lymphocyte antigen-4 (CTLA-4) blocking antibody) was initiated. One month later, he was admitted for the 2nd cycle of ipilimumab. On admission, he presented right cervical lymphadenopathy, painful severe hepatomegaly and altered liver tests (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase and alkaline phosphatase) with elevated C-reactive protein (Table 1).

Liver ultrasonography showed an heterogeneous hepatomegaly without focal lesion and no signs of obstruction. An empirical antibiotic treatment was initiated without clinical improvement. In addition, bacterial, viral and auto-immune investigations were negative.

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography was performed in order to evaluate the response to ipilimumab and to exclude any inflammatory and/or infectious foci. Compared to the baseline examination, an intense and diffuse metabolic activity involving the entire hepatic parenchyma, as well as multiple cervical and mediastinal lymph nodes were evidenced (Figure 1).These hepatic findings suggested an ipilimumab-induced hepatitis versus a diffuse metastatic infilt-

Table 1. Biochemical parameters

Biochemical parameters (Normal values)	Day1	Day4	Day6	Day8	Day10
AST (<40UI/L)	70	82	180	166	201
ALT(6-49UI/L)	94	93	125	112	90
GGT(8-61UI/L)	177	290	256	214	196
ALP(40-130UI/L)	304	521	474	379	322
Total Bilirubin (<1.2mg/dL)	0.9	1.1	1.6	2.2	2.6
LDH(240-480UI/L)	974	1073	1446	2202	-
PTT(70-100%)	97.4	105.7	-	66	67.1
Urea(13-47mg/dL)	60	63	132	197	217
Creatinin(0.72-1.17mg/dL)	1.04	1.00	1.92	2.39	2.65
Bicarbonate(23-30mmol/L)	22	22	10	8	9
Kaliaemia(3.4-4.5mmol/L)	4.6	4.9	5.5	5.0	4.3
Leukocytosis(3.5-11.0x10^3/μL)	10.39	11.51	13.28	19.96	16.68
CRP (0.1-10 mg/L)	228.3	282.5	318.2	319.8	244.0

AST=aspartate aminotransferase ; ALT=alanine aminotransferase ; GGT= gamma-glutamyl transpeptidase ; ALP= alkaline phosphatase; LDH= lactate dehydrogenase ;PTT=prothrombin time ; CRP= C-reactive protein

ration. A corticotherapy was initiated (125mg of methylprednisolone/day administered orally) and a percutaneous liver biopsy of the left lobe was performed. Anatomopathology confirmed the metastatic infiltration state with melanoma cells, positive for S100, Melan-A and cytokeratin A1 and A3 in the immunohistochemical analysis (Figure 2).

The patients clinical condition rapidly deteriorated with the development of acute renal failure, acid-basic, electrolytic and coagulation disorders (Table 1). He was eventually transferred to the intensive care unit on his 8th hospitalization day and finally deceased 4 days later due to severe hepatic failure.

Discussion

Malignant melanomas represent 5% of all skin neoplasias [1], however the incidence of melanoma is rising over the last years. Liver metastases are observed in 10%-20% of patients with melanoma and are associated with poor prognosis and short survival rate [2]. The majority of patients present focal liver lesions or nodular liver infiltration.

Few cases of diffuse melanoma liver infiltration have been reported so far [3-11]. Morphological imaging techniques (ultrasonography, CT or MRI) failed to detect diffuse infiltration in those cases, showing only hepatomegaly without any individual lesion and final diagnosis was confirmed on liver biopsy. On the contrary, the metabolic information provided by the ^{18}F-FDG PET/CT suggested an hepatic infiltration status prior to biopsy.

An intense hepatic ^{18}F-FDG uptake has also been reported in patients treated with ipilimumab, a cytotoxic T-lymphocyte antigen-4 blocking antibody. Ipilimumab can induce immune-related adverse events (such as hepatitis), in up to 9% of patients [12].

Diffusely increased ^{18}F-FDG liver uptake has been described in ipilimumab induced hepatitis [13] as well as in other

neoplasic pathologies such as breast cancer, Hodgkin's disease, chronic myeloid leukemia, small cell lung carcinoma, hepatocellular carcinoma in infectious pathologies line, tuberculosis, Q fever [14-20].

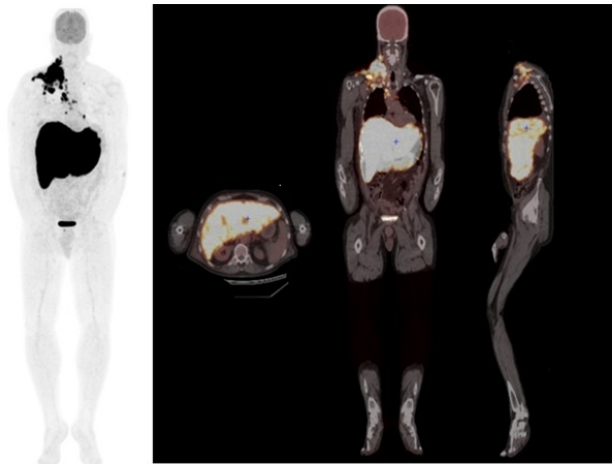

Figure 1. Intense and diffuse metabolic activity involving the entire hepatic parenchyma, the cervical and mediastinal lumph nodes on ^{18}F-FDG PET/CT scan.

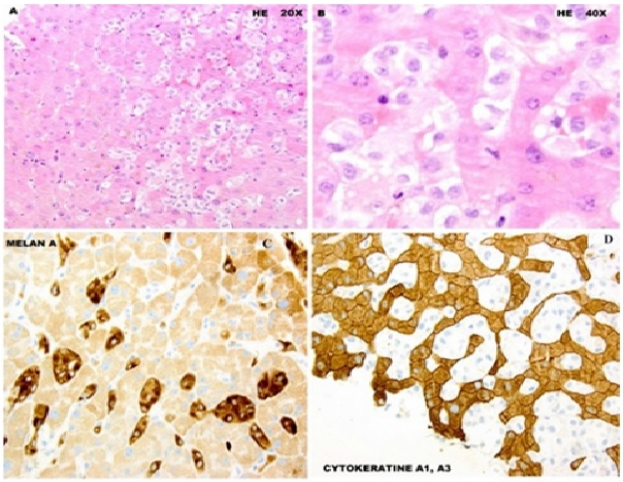

Figure 2. A) Hematoxylin-cosin stain of melanoma. Original magnification 20x. B) Hematoxylin-cosin stain of melanoma. Original magnification 40x. C) Specimen stained with Melan A immunohistochemistry. Original Magnification 40x. D) Specimen stained with cytokeratine A1 and A3 immunohistochemistry. Original magnification 40x.

To the best of our knowledge, this is the first report of a melanoma diffuse liver metastatic infiltration evidenced with ^{18}F-FDG PET/CT.

In conclusion, we report here the first case of diffuse hypermetabolic liver uptake on ^{18}F-FDG PET/CT due to diffuse metastatic infiltration in a melanoma patient treated with ipilimumab. Such image pattern does not necessary mean autoimmune adverse event (hepatitis). This case demonstrates that a liver biopsy must be performed in order to exclude neoplasic liver infiltration when facing a diffuse hypermetabolic liver uptake.

Bibliography

1. National Collaborating Centre for Cancer, Guidance on Cancer Services: *Improving Outcomes for People with Skin Tumours including Melanoma;* The Manual, Vol. 2009. National Institute for Health and Clinical Excellence, London, 2006.
2. Rose DM, Essner R, Hughes TD et al. Surgical resection for metastatic melanoma to the liver. The John Wayne Cancer Institute and Sydney Melanoma Unit Experience. *Arch Surg* 2001; 136; 950-5.
3. J Montero JL, Muntane J, de las Heras S et al. Acute liver failure caused by diffuse hepatic melanoma infiltration. *Hepatol* 2002; 37: 540-1.
4. Shan GD, Xu GQ, Chen LH et al. Diffuse liver infiltration by melanoma of unknown primary origin: one case report and literature review. *Intern Med* 2009; 48 (24): 2093-6.
5. Bouloux PM, Scott RJ, Goligher JE, Kindell C. Fulminant hepatic failure secondary to diffuse liver infiltration by melanoma. *Journal of the Royal Society of Medicine* 1986; 79(5) :302-3.
6. Tanaka M, Watanabe S, Masaki T et al. Fulminant hepatic failure caused by malignant melanoma of unknown primary origin. *J Gastroenterol* 2004; 39: 804-6.
7. Te HS, Schiano TD, Kahaleh M et al. Fulminant hepatic failure secondary to malignant melanoma: case report and review of the literature. *Am J Gastroenterol* 1999; 94: 262-6.
8. Pichon N, Delage-Corre M, Paraf F. Hepatic metastatic miliaria from a malignant melanoma: 2 case reports. *Gastroenterol Clin Biol* 2004; 28: 593-5.
9. Rubio S, Barbero-Villares A, Reina T et al. Rapidly-progressive liver failure secondary to melanoma infiltration. *Gastroenterol Hepatol* 2005; 28: 619-21.
10. Fusasaki T, Narita R, Hiura M et al. Acute hepatic failure secondary to extensive hepatic replacement by metastatic amelanotic melanoma: an autopsy case report. *Clin J of Gastroenterol* 2010; 3(6): 327–31.
11. Kaplan GG, Medlicott S, Culleton B, Laupland KB. Acute hepatic failure and multi-system organ failure secondary to replacement of the liver with metastatic melanoma. *BMC Cancer* 2005, 5:67.
12. Voskens CJ, Goldinger SM, Loquai C et al. The Price of Tumor Control: An Analysis of Rare Side Effects of Anti-CTLA-4 Therapy in Metastatic Melanoma from the Ipilimumab Network. *PLoS ONE* 2013; 8(1): e53745.
13. Raad RA, Pavlick A, Kannan R, Friedman KP. Ipilimumab-Induced Hepatitis on ^{18}F-FDG PET/CT in a Patient with Malignant Melanoma. *Clin Nucl Med* 2015; 40(3): 258-9.
14. Tichelaar V, Gemmel F, de Rhoter W et al. FDG hepatic superscan caused by massive breast cancer invasion. *Clin Nucl Med* 2009; 34(10): 716-8.
15. Wong SS, Yuen HY, Ahuja AT. Hepatic tuberculosis: a rare cause of fluorodeoxyglucose hepatic superscan with background suppression on positron emission tomography. *Singapore Med J* 2014; 55(7): e101-3.
16. Du B, Li X, Li N et al. ^{18}F-FDG hepatic superscan in a patient with chronic myeloid leukemia. *Clin Nucl Med* 2014; 39(9): 835-6.
17. Basu S, Nair N. Unusually elevated liver radioactivity on F-18 FDG PET in Hodgkin's disease: hepatic "superscan". *Clin Nucl Med* 2004; 29(10): 626-8.
18. Trojan J, Schroeder O, Raedle J et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. *Am J Gastroenterol* 1999; 94: 3314-9.
19. Oh M, Baek S, Lee SO et al. A Case of Acute Q Fever Hepatitis Diagnosed by F-18 FDG PET/CT. *Nucl Med Mol Imaging* 2012; 46(2): 125-8.
20. Zhou W, Zhao J, Xing Y et al. Diffuse Hepatic Amebiasis Detected by FDG PET/CT. *Clin Nucl Med* 2015; 40(2): e167-70.