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

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

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 a 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 infiltr-
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 18F-FDG PET/CT suggested an hepatic infiltration status prior to biopsy.

An intense hepatic 18F-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 18F-FDG liver uptake has been described in ipilimumab induced hepatitis [13] as well as in other

<table>
<thead>
<tr>
<th>Biochemical parameters (Normal values)</th>
<th>Day1</th>
<th>Day4</th>
<th>Day6</th>
<th>Day8</th>
<th>Day10</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (&lt;40UI/L)</td>
<td>70</td>
<td>82</td>
<td>180</td>
<td>166</td>
<td>201</td>
</tr>
<tr>
<td>ALT(6-49UI/L)</td>
<td>94</td>
<td>93</td>
<td>125</td>
<td>112</td>
<td>90</td>
</tr>
<tr>
<td>GGT(8-61UI/L)</td>
<td>177</td>
<td>290</td>
<td>256</td>
<td>214</td>
<td>196</td>
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<tr>
<td>ALP(40-130UI/L)</td>
<td>304</td>
<td>521</td>
<td>474</td>
<td>379</td>
<td>322</td>
</tr>
<tr>
<td>Total Bilirubin (&lt;1.2mg/dL)</td>
<td>0.9</td>
<td>1.1</td>
<td>1.6</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>LDH(240-480UI/L)</td>
<td>974</td>
<td>1073</td>
<td>1446</td>
<td>2202</td>
<td>-</td>
</tr>
<tr>
<td>PTT(70-100%)</td>
<td>97.4</td>
<td>105.7</td>
<td>-</td>
<td>66</td>
<td>67.1</td>
</tr>
<tr>
<td>Urea(13-47mg/dL)</td>
<td>60</td>
<td>63</td>
<td>132</td>
<td>197</td>
<td>217</td>
</tr>
<tr>
<td>Creatinin(0.72-1.17mg/dL)</td>
<td>1.04</td>
<td>1.00</td>
<td>1.92</td>
<td>2.39</td>
<td>2.65</td>
</tr>
<tr>
<td>Bicarbonate(23-30mmol/L)</td>
<td>22</td>
<td>22</td>
<td>10</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Kaliaemia(3.4-4.5mmol/L)</td>
<td>4.6</td>
<td>4.9</td>
<td>5.5</td>
<td>5.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Leukocytosis(3.5-11.0x109/µL)</td>
<td>10.39</td>
<td>11.51</td>
<td>13.28</td>
<td>19.96</td>
<td>16.68</td>
</tr>
<tr>
<td>CRP (0.1-10 mg/L)</td>
<td>228.3</td>
<td>282.5</td>
<td>318.2</td>
<td>319.8</td>
<td>244.0</td>
</tr>
</tbody>
</table>

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

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 neoplastic liver infiltration when facing a diffuse hypermetabolic liver uptake.

Bibliography