A remarkable case of extranodal Hodgkin lymphoma monitored with F-18 FDG PET/CT

Nick Damien van Rijsewijk, Azzam Abdalla Ibrahim, Peter Smeets, Ingeborg Goethals

ABSTRACT

Although lymphomas are typically defined by enlarged lymph nodes and the involvement of other lymphoid tissues, Hodgkin’s disease may rarely present with extranodal disease. F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is the current state-of-the-art imaging technique in evaluating (Hodgkin) lymphoma and is very appropriate to reveal extranodal disease. In this case, the diagnostic PET/CT scan shows that, in addition to numerous enlarged and metabolically active lymph nodes, non-lymphoid organs are also affected. In particular, the involvement of the stomach wall and the pancreas is exceptional. Furthermore, this case reflects well the value of F-18 FDG PET/CT imaging during and after treatment.

Keywords: Extranodal disease, F-18 FDG PET/CT, Hodgkin lymphoma, (Re)staging

INTRODUCTION

Although Hodgkin lymphomas (HLs) are normally characterized by enlarged lymph nodes and the involvement of other lymphoid tissues, also non-lymphoid organs may be involved. In this case report, we will elaborate on the role of F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in staging and restaging of HL based on an advanced presentation.

CASE REPORT

A 49-year-old man presented in the hospital with a dry cough that persisted for several months, and since a few days, he additionally suffered from heavy night sweats, fever, and extreme fatigue with no apparent cause. The clinical examination revealed enlarged lymph nodes in the neck and the axilla bilaterally. Analysis of a peripheral blood sample showed an inflammatory tableau. A CT scan of the thorax now showed a large mass in the mediastinum and also many enlarged supra- and infradiaphragmatic lymph nodes. This time, the patient consented to an excisional biopsy at the right axilla. The histological diagnosis of classical HL of the nodular sclerosing type was made.

For staging purposes, an F-18 FDG PET/CT examination was performed and showed numerous intensely F-18 FDG-avid lymph nodes, both supra- and infradiaphragmatically (Figure 1A). However, various other organs and tissues were also involved, namely the parotid glands, the lung parenchyma (bilateral), the stomach wall, the spleen parenchyma, the pancreas, and
the left adrenal gland (Figures 2 and 3). There was also increased F-18 FDG uptake in the bone marrow of the axial skeleton. A stage 5 disease according to the Deauville classification was made (Table 1).

ABVD chemotherapy (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) was started (6 cycles). To evaluate an early therapy response, an interim F-18 FDG PET/CT examination was conducted after two cycles of chemotherapy. A partial metabolic response was seen with residual metabolically active disease in the anterior mediastinum and the lung hilus bilaterally, albeit significantly decreased compared with the diagnostic PET/CT findings, equaling a Deauville score of 4 (Figure 1B). Hence, second-line chemotherapy, namely escalated BEACOPP chemotherapy (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone) was started. After the completion of a total of 6 cycles (with 50% reduction of bleomycin dosage from cycle 3 on due to suspected lung toxicity), a repeat PET/CT was performed and showed a complete metabolic therapy response (Figure 1C). New lung consolidations appeared, however, were deemed to be of infectious origin.

A novel F-18 FDG PET/CT was acquired after three months. Metabolically active disease in the mediastinum was documented (Figure 4A). Therefore, a thoracoscopic biopsy was performed. Relapse of HL was diagnosed for which DHAP (Dexamethasone, high dose Ara-C, and Platinol) was introduced. A new interim PET/CT examination was made after two cycles, which showed progressive disease with evolving CT-graphic and metabolic lesions in the left lung equaling a Deauville score of 5 (Figure 4B). Therefore, Brentuximab vedotin (Adcetris) was started. After 4 cycles, the therapy was discontinued due to the occurrence of immunotherapy-related disease, in particular nodular pulmonary infiltrates. Also, elevated metabolic activity was seen in the right scapula, for which there was no CT correlate (Figure 5).

After a three-month therapy break and before pembrolizumab was initiated, again, an F-18 FDG PET/CT examination was performed. Stable disease was documented (Figure 6A). After 8 cycles of pembrolizumab, the patient underwent another F-18 FDG PET/CT examination. Partial therapy response was documented with a Deauville score of 4 (Figure 6B). Hence, bendamustine was added to the treatment regimen. After 4 cycles of pembrolizumab-bendamustine, a repeat F-18 FDG PET/CT was performed. Complete treatment response was documented (Figure 6C) and allogeneic stem cell transplantation with an unrelated donor was planned after six weeks of washout of pembrolizumab. Before transplantation, F-18 FDG PET/CT showed persistent complete remission with a Deauville score of 2.

One month after allogeneic stem cell transplantation, a severe graft-versus-host reaction was successfully treated with beclomethasone and Entocort. However, invasive pulmonary aspergillosis developed, for which the patient eventually needed respiratory and hemodynamic support. Nevertheless, overall secondary organ failure occurred and the patient died four years after the first hospital admission.

**DISCUSSION**

Lymphomas are characterized by enlarged lymph nodes and the involvement of other lymphoid tissues.
Non-lymphoid organs may also be involved, which is known as extranodal disease [1]. However, extranodal disease is relatively rare (up to 15%) in HL [2–4]. This case illustrates a rare first presentation of an advanced HL on F-18 FDG PET/CT examination, namely with the involvement of the parotid glands, lung parenchyma, gastric wall, spleen parenchyma, pancreas, left adrenal gland as well as the bone marrow of the axial skeleton as well as numerous intensely metabolically active lymph nodes. To the best of our knowledge, the involvement of the stomach wall and the pancreas has never been described before.

F-18 FDG PET/CT is the current state-of-the-art imaging technique in staging HL. Moreover, because it is a full-body examination, F-18 FDG PET/CT is particularly suitable for detecting extranodal disease [5]. In addition to a visual interpretation of the tracer distribution, F-18 FDG uptake is also measured by the standard uptake value (SUV), which is the image-derived radioactivity concentration relative to the injected radioactivity per kg body weight and correlates with the severity of the

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tr>
<td>1</td>
<td>No tracer uptake</td>
</tr>
<tr>
<td>2</td>
<td>Tracer uptake less than or equal to the uptake in the mediastinum.</td>
</tr>
<tr>
<td>3</td>
<td>Tracer uptake higher than that of the mediastinum but lower than or equal to that of the liver.</td>
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<tr>
<td>4</td>
<td>Moderately increased tracer uptake compared to liver.</td>
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<tr>
<td>5</td>
<td>Strongly increased tracer uptake (&gt;2–3× SUV_{max} of normal liver) compared to liver and/or new lesions.</td>
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Abbreviation: SUV_{max}: Maximum standard uptake value.
disease [5, 6]. For this reason, the maximum SUV is often used as a guide to identifying the most appropriate biopsy site [5].

Moreover, F-18 FDG PET/CT combines the high sensitivity of F-18 FDG PET with the high specificity of CT [6], with a sensitivity and specificity of 90% and 91%, respectively, for the hybrid imaging modality [7]. The value of the F-18 FDG PET/CT examination is corroborated by a change in disease stage in 10–30% of patients compared to staging with CT alone. In addition, in HL, this is usually an upstaging to a higher disease stage [6]. This occurs in the order of 14% and is mainly due to the presence of increased F-18 FDG activity in the bone marrow and/or in lymph nodes that are not enlarged on CT [5]. Downstaging after F-18 FDG PET/CT examination occurs in 6% of patients with HL, mainly when there is no increased F-18 FDG uptake in an enlarged spleen and/or enlarged lymph nodes described on CT [5]. Hence, national and international guidelines of the European Society for Medical Oncology (ESMO) recommend total body F-18 FDG PET/CT examination for staging purposes [8, 9].

Also, for the detection of extranodal disease, F-18 FDG PET/CT has a higher sensitivity and specificity than diagnostic CT (performed with the administration of intravenous contrast), namely 88% and 100% versus 50% and 90%, respectively. This is especially true for HL located in the mucosa, the cortical bone, the bone marrow, the lungs, the pleura, and the gastrointestinal tract [4]. However, all organs and tissues may be involved [5].

A gastrointestinal localization of extranodal disease, as in our case, is almost exclusively found in non-Hodgkin lymphoma (NHL) types, namely in 10–30% of all NHL [4]. Involvement of the pancreas, as in our case, is extremely rare and in the vast majority of cases, due to invasion of the pancreas by adjacent lymph nodes [2]. In our case, a “true” HL involvement of the pancreatic parenchyma was diagnosed (Figure 2).

At diagnosis, the bone marrow is involved in approximately 5–14% of all HL. In untreated patients, a higher uptake of F-18 FDG in the bone marrow compared to the uptake in the liver parenchyma is indicative of bone marrow invasion. Interestingly, the incidence of bone marrow invasion increases later in the course of the disease and F-18 FDG PET/CT may show diffuse, as in our case, or focally increased metabolic activity in the bone marrow. Importantly, diffusely increased treatment-related uptake due to chemotherapy or granulocyte colony-stimulating factor (G-CSF) (in case of response to this therapy) must be discriminated from bone marrow invasion [1].

Extranodal sites in the head and neck region occur in less than 1% of all HL cases [2]. Parotid gland involvement in HL, as in our case, is therefore exceptional.

In HL, the lung parenchyma is involved in 6–11% of cases, occurring bilaterally in about 4%. The lung is more often involved in disease relapse than at primary diagnosis and is usually associated with enlarged hilar and mediastinal lymph nodes [2]. In this case, the lung parenchyma was affected bilaterally at primary diagnosis.

The spleen is considered a nodal organ in HL [2, 3]. The tracer uptake can be diffusely increased, but can also show intense focal spots, a large solitary mass or a mixed pattern (as in our case) [3, 10]. The sensitivity and specificity of F-18 FDG PET/CT are 100% for diagnosing primary involvement of the spleen. Post-therapy sensitivity decreases due to possible reactive tracer uptake [3]. It is noteworthy that the size of the spleen, as measured on CT, is not a reliable diagnostic parameter [2].

Interim F-18 FDG PET/CT after two cycles of ABVD in HL, as performed in our patient, has a very high prognostic value for progression-free survival: after two years, 96% of patients with a negative PET/CT do not recur, whereas an abnormal F-18 FDG PET/CT examination has a recurrence rate of 100%. These findings have led to the adjustment of therapy based on the interim PET/CT as well as the introduction of the Deauville criteria [5] (Table 1). The Lugano classification, which is a lymphoma staging system, recommends this five-point scale for reporting response [10].

The current cut-off value for a change of treatment is situated between 3 and 4 points according to the Deauville scale, with a score of 3 or lower equaling a PET-negative result and a score of 4 or higher equaling a PET-positive result [6]. The Lugano classification uses this cut-off also, with a score of 3 or lower equaling complete metabolic response. A score of 4 or 5 can be considered as a partial metabolic response (reduced FDG uptake compared with baseline and residual mass(es)) or no metabolic response (no significant reduction in FDG uptake) [10]. As such, the national and ESMO guidelines recommend changing chemotherapy in a PET-positive interim F-18 FDG PET/CT. As a result, it is recommended to intensify treatment to escalated BEACOPP when after 2 cycles of ABVD the Deauville score equals 4, as in our case [8, 9].

End-of-treatment assessment is more accurate with F-18 FDG PET/CT compared to CT [10]. If PET/CT after completing treatment does not show residual metabolic activity, a favorable outcome is expected. Negative PET/CT at the end of treatment has a high negative predictive value (94%) regardless of the size of any residual masses on CT [5]. At the end of treatment with escalated BEACOPP, complete remission was observed in our patient.

Surveillance scans after complete remission are not recommended by the ESMO guidelines and should only be performed based on clinical suspicion [8]. Nevertheless, repeat PET/CT is often performed to follow up unequivocal results.

CONCLUSION

This case illustrates a rare presentation of an advanced HL on F-18 FDG PET/CT with an exceptional extranodal involvement of the stomach and the pancreas. In addition, the value of F-18 FDG PET/CT imaging during
REFERENCES


Author Contributions

Nick Damien van Rijsewijk – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Azzam Abdalla Ibrahim – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Peter Smeets – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ingeborg Goethals – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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