Rare ocular and skin lesions of Marginal Zone Lymphoma detected by ^{18}F-FDG PET/CT

Case Report

Corinna Altini[1], Artor Niccoli Asabella[1], Cristina Ferrari[1], Domenico Rubini[1], Antonia Gentile[2], Giuseppe Rubini[1]

[1]Nuclear Medicine Unit, DIM., University of Bari "Aldo Moro", Bari, Italy
[2]Pathological Anatomy Unit, DAP, University of Bari "Aldo Moro", Bari, Italy

(Received 31 January 2014, Revised 16 February 2014, Accepted 18 February 2014)

ABSTRACT

We report a case of a 75-year old man that came at hematologist's attention for lymphoma evaluation due to axillary lymph node enlargement and fever. Thorax, abdomen and pelvis Contrast-Enhanced Computed Tomography (CECT) showed lymph nodes, spleen and liver lesions. Axillary lymph node biopsy was performed and the diagnosis of marginal zone lymphoma (MZL) at stage IV was postulated, then the patient was submitted to chemotherapy (CHT) following the R-CVP scheme. After the end of the eighth cycle of CHT he was submitted to a restaging CECT that showed lymph nodes size reduction in all the sites identified on the staging exam. Furthermore the liver lesions disappeared and spleen lesions size was reduced. A whole-body and head ^{18}F-FDG PET/CT was also performed that showed ^{18}F-FDG uptake lesions in right axillary lymph nodes, spleen and liver and the identification of two more extranodal sites, respectively in conjunctiva and skin. Then the necessity of additional CHT cycles and radiotherapy on extranodal sites was postulated. The patient declined the new therapies and unfortunately succumbed four months later.

In our case whole body and head ^{18}F-FDG-PET/CT, finding two new extranodal lymphomatous sites and confirming the persistence of the disease, refined and guided the management of the patient suggesting the necessity of additional CHT cycles and radiotherapy on extranodal sites.

After histopathological confirmation, a systemic work-up by an oncologist should include whole body and head ^{18}F-FDG-PET/CT to detect possible systemic involvement and guide specific following diagnostic exams.

Key words: ^{18}F-FDG PET/CT; Marginal zone lymphoma; conjunctiva; skin

Iran J Nucl Med 2014;22(2):89-93
Published: June, 2014
http://irjnm.tums.ac.ir

Corresponding author: Artor Niccoli Asabella, Piazza G. Cesare 11, 70124 Bari, Italy.
E-mail: artor.niccoliasabella@uniba.it

INTRODUCTION

Marginal zone lymphoma (MZL) is a subgroup of indolent B-cell Non Hodgkin Lymphomas (NHLs) originating from cells of the 'marginal zone' of the secondary lymphoid follicle.

MZL is the third most common NHL accounting for 5-17% of all NHLs, comprises 7%-8% of all B-cell lymphomas and includes 3 specific entities: extranodal marginal zone lymphoma (EMZL), also called mucosa-associated lymphatic tissue (MALT) lymphoma, splenic MZL (SMZL) and nodal MZL (NMZL) [1].

EMZL is the most common entity, accounting for approximately 70% of all MZLs. The most common localization is the gastrointestinal tract but salivary glands, thyroid gland, ocular orbitae, breast, lung and skin can be involved [2]. SMZL accounts for approximately 20% of all MZLs, while NMZL is the less common entity (10%) [1].

Across studies, roughly half of the patients present with stage III or IV disease. Each site of the disease can be involved as primary or secondary localization, so despite advances in MZL classification, patients with generalized disease at diagnosis cannot be ascribed easily to a precise diagnostic group [1, 3].

Clinical presentation of MZL is non-specific and highly variable and B symptoms are present in 10-20% of patients [4].

Systemic staging evaluations involve a physical examination (e.g., for lymphadenopathy), complete blood count (with differential), bone marrow biopsy, and Contrast-Enhanced Computed Tomography (CECT) imaging of the chest and abdomen [5].

18-fluoro-2-deoxyglucose positron emission tomography/computer tomography (^{18}F-FDG PET/CT) is a whole-body technique, which can characterize the metabolic behavior of morphologic changes.

^{18}F-FDG PET/CT today is performed widely in neoplastic diseases, demonstrating its validity even in comparison with other imaging modalities [6].

^{18}F-FDG PET/CT is currently regarded as the reference standard in the imaging of the majority of lymphoma type, for evaluation of nodal and extra-nodal distribution of the disease by providing both functional and anatomic information in a single whole body examination [7].

^{18}F-FDG PET/CT role is well established in Hodgkin Disease and aggressive NHL, but its impact on the other histotypes remains to be defined, in particular data regarding indolent lymphoma are more controversial [3, 8, 9]. Here we report a case of a patient with two unusual secondary localizations of MZL identified by ^{18}F-FDG PET/CT.

CASE REPORT

A 75-year old male came at hematologist's attention for lymphoma evaluation due to axillary lymph node enlargement and fever. Axillary ultrasonography described very firm, rounded and rubbery lymph nodes with maximum diameter of 30 mm.

The patient's previous clinical history was significant just for heart disease.

Blood tests showed white blood cell of 10.62 x 10^3/microl (range 4- 9.5), lymphocytes of 46.9% (range 20-45), lactate dehydrogenase level of 421 IU/l (n.v. 140-280) and erythrocyte sedimentation rate of 39 mm/h (range for old people: < 35).

A thorax, abdomen and pelvis CECT was performed to stage the disease, revealing multiple rounded enlarged lymph nodes in both axillae (more evident in the right one) with maximum diameter of 30 mm. Other enlarged lymph nodes were observed in right pulmonary hilum, in mesenterial site and in inguinal site bilaterally. Focal lesions due to lymphoma localizations were also observed in liver and spleen.

After an axillary lymph node biopsy the diagnosis of MZL at stage IV was postulated and the patient was submitted to chemotherapy (CHT) following the R-CVP scheme.

After the end of the eighth cycle of CHT he was submitted to a thorax, abdomen and pelvis CECT that showed lymph nodes size reduction in all the sites identified on the staging CECT. Furthermore the liver lesions disappeared and spleen lesions size was reduced.

Meanwhile the patient's clinical conditions were stable, except for the appearance of left eyelid swelling.

To confirm the actual response to CHT a whole-body and head ^{18}F-FDG PET/CT was also performed. The whole body scan (Figure 1) showed high ^{18}F-FDG uptake in right axilla lymph nodes (SUV max 10.1), in an area in the 7th liver segment (SUV max 4.9) and in two areas in the spleen (SUV max 3.4). Furthermore high ^{18}F-FDG uptake area was observed subcutaneously in the right dorsal region, in front of the scapula's spine and the infraspinatus muscle (SUV max 8.2).

Moreover the head ^{18}F-FDG PET/CT scan (Figure 2) showed high ^{18}F-FDG uptake area in the lateral side of the left orbital cavity (SUV max 5.6).

Due to the suspect of extranodal sites of NHL, biopsies of the subcutaneous lesion and of the left conjunctiva were performed. The microscopy and immunocytological analysis (Figure 3) confirmed the MZL localizations in both sites.

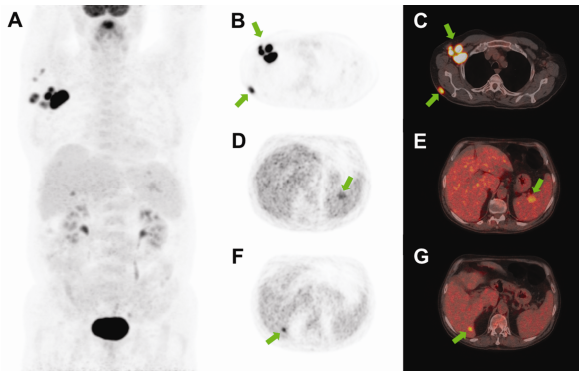

Fig 1. Whole-body ^{18}F-FDG PET/CT MIP (A), transaxial PET and fused PET/CT (B-G) images show high ^{18}F-FDG uptake areas in right axilla lymph nodes, in the right dorsal region, in spleen and in the 7th liver segment (green arrows).

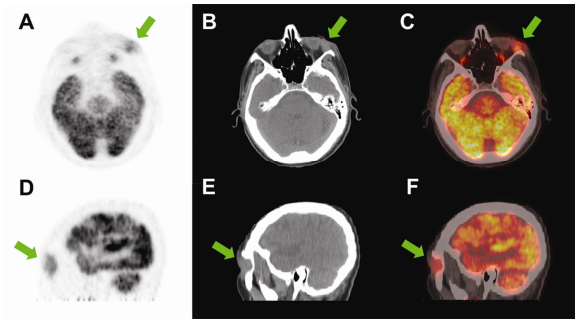

Fig 2. head ^{18}F-FDG PET/CT transaxial PET (A, D), CT (B, E) and fused PET/CT (C, F) images show high ^{18}F-FDG uptake area in the lateral side of the left orbital cavity (green arrows).

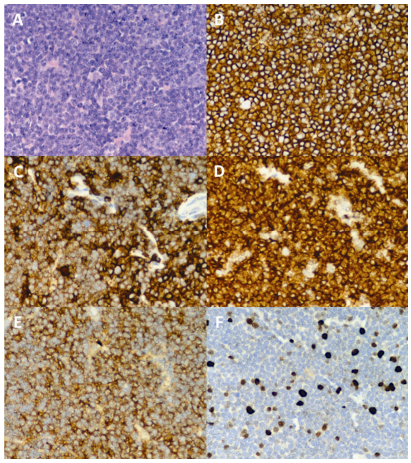

Fig 3. The histological analysis of left conjunctiva specimen showed (A) a diffuse infiltrate of monomorphous, medium size cells with vesicular chromatin (BL cells) (hematoxylin and eosin stain, original magnification 200x). The lymphomatous infiltrate exhibits (B) a characteristic expression of pan B-cell marker CD20 (immunoperoxidase, original magnification 200x) and the neoplastic B cells express (C) CD43 (200x), (D) bcl2 (200x) and (E) lambda chain (200x). The Ki 67 labeling index (F) approaches more than 20% (immunoperoxidase, original magnification 200x).

The identification of ^{18}F-FDG uptake in two new extranodal sites and in areas corresponding to the known disease sites led to the observation of poor response to therapy and the necessity of additional CHT cycles and radiotherapy on extranodal sites.

The patient declined the new therapies and unfortunately succumbed four months later.

DISCUSSION

Extranodal involvement can be seen in lymphoma patients in approximately 25-40% of cases and almost any organ can be involved [10].

Orbital lymphomas constitute approximately 8% of extranodal NHL and represents 5% of systemic non-Hodgkin's disease [10].

More than 95% of orbital lymphomas are B-cell origin and, of those, approximately 80% are low-grade lymphomas; MZL constitutes the majority of the histological variants [10-12].

The most common sites of ocular involvement are the orbit (40%), conjunctiva (35 to 40%), lacrimal gland (10 to 15%), and the eyelid (around 10%) and are bilateral in 10-15% of cases.

Early conjunctival lymphoma typically doesn't present pain or oculomotor signs as well as in our patient in which, despite the stage IV, no ocular symptoms were present at the diagnosis but, as the disease proceeded, left eyelid edema occurred [13].

Cutaneous lymphomas are mostly T-cell NHL, constituting up to 65% of cases. Skin involvement in B-cell NHL is seen in up to 25% of cases of which MZL represents the 59% [10, 14]. It is important to distinguish primary cutaneous lymphomas from systemic lymphomas secondarily involving the skin because of the better prognosis (primary cutaneous lymphomas tends to follow an extremely indolent course), different disease associations, and alternative staging schemes and treatment options [15]. In our patient the lack of skin lesions at the staging suggested the secondary skin involvement by MZL, characterized by worse prognosis and confirmed by the forthcoming patient outcome.

Also spleen and liver involvement in MZL can be primary or secondary, with single or multiple nodular lesions. Identifying them as secondary sites lead to the diagnosis of advanced stage disease (IV) with consequent change of treatment strategy [10].

How to differentiate the 3 entities of MZL in advanced stages remains a key point of debate. Distinguishing between disseminated lymphnodal disease involving extranodal sites and primary extranodal disease is challenging. [10]

Overall, the histologic and immunohistochemical differences in MZL are subtle and in general

insufficient to reliably distinguish primary from secondary disease. Both types also have an identical immunophenotype being CD43+, BCL2+, CD10- and BCL6- [15].

Furthermore, because MZL presents with disseminated disease in 25-50% of cases and clinical presentations may be considerable overlapped for patients with primary and secondary extranodal disease, it is reasonable to perform a systemic evaluation for all patients [1, 15].

^{18}F-FDG PET/CT has a pivotal role in evaluating patients with lymphoma [10]. Many studies demonstrated the utility of ^{18}F-FDG PET/CT imaging for Hodgkin's disease and NHL with sensitivity close to 100% in aggressive NHL, otherwise ^{18}F-FDG PET/CT seems to be less sensitive in detecting indolent NHL [3, 8].

In literature are reported data that demonstrate lower ^{18}F-FDG uptake in indolent NHL [3]. Beal et al reported that low-grade NHLs are less FDG avid, but enough to be detected by ^{18}F-FDG PET/CT, in particular they found high ^{18}F-FDG avidity in the majority (80%) of MZL cases. For these reasons the utility of ^{18}F-FDG PET/CT scans in the staging of MZL remains still under debate [8].

^{18}F-FDG PET/CT sensitivity in MZL seems to be related to sites involvement and stage of disease: extra-gastric and advanced disease at the time of diagnosis (stage III-IV, according to Ann Arbor classification) more correlates with high ^{18}F-FDG uptake rather than gastric localization and early disease (stage I-II) [3].

According literature, in the patient we described with MZL stage IV at diagnosis, ^{18}F-FDG PET/CT showed high sensitivity and specificity, revealing correctly nodal and extranodal disease localizations.

In addition, the standardized uptake value (SUV), a semiquantitative index of ^{18}F-FDG uptake may help in determining disease aggressiveness, and predicting patients outcome [9, 16]. Many reports show a correlation between high ^{18}F-FDG uptake and high histologic grade of lymphoma [8].

In the case we presented, despite the low-grade histology, all the lesions showed a relatively high ^{18}F-FDG uptake, demonstrating disease aggressiveness confirmed by the poor prognosis of the patient.

^{18}F-FDG PET/CT has more relevant role in stratifying treatment response and assessing post-treatment surveillance in lymphoma patients, even in MZL that show relatively high systemic relapse rates (14-43%) [2, 3].

The change in the therapy strategy is the most important measurable outcome; ^{18}F-FDG PET/CT changed the management in 71% of the secondary MZL patients, detecting viable sites of active systemic disease, providing whole body screening, and guiding specific diagnostic studies (directing MRI-CT, expert assessment, bone marrow biopsy, etc.) in selected cases [17].

In our case whole body and head ^{18}F-FDG-PET/CT, finding two new extranodal lymphomatous sites and confirming the persistence of the disease, refined and guided the management of the patient suggesting the necessity of additional CHT cycles and radiotherapy on extranodal sites.

CONCLUSION

This case reveals the need of whole body and head ^{18}F-FDG PET/CT metabolic evaluation also in patients with indolent NHL in order not to miss exceptional sites involvement and to confirm the malignant potential. ^{18}F-FDG PET/CT plays an increasingly important role in clinical decision-making; it may change the management of MZL, suggesting the optimal treatment programs for each patient. After histopathological confirmation, a systemic work-up by an oncologist should include whole body and head ^{18}F-FDG-PET/CT to detect possible systemic involvement and guide specific following diagnostic exams.

REFERENCES

1. Zinzani PL. The many faces of marginal zone lymphoma. Hematology Am Soc Hematol Educ Program. 2012;2012:426-32.
2. Deinbeck K, Geinitz H, Haller B, Fakhrian K. Radiotherapy in marginal zone lymphoma. Radiat Oncol. 2013 Jan 2;8:2.
3. Perry C, Herishanu Y, Metzer U, Bairey O, Ruchlemer R, Trejo L, Naparstek E, Sapir EE, Polliack A. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. Eur J Haematol. 2007 Sep;79(3):205-9.
4. van den Brand M, van Krieken JH. Recognizing nodal marginal zone lymphoma: recent advances and pitfalls. A systematic review. Haematologica. 2013 Jul;98(7):1003-13.
5. Reid R1, Friedberg JW. Management of marginal zone lymphoma. Oncology (Williston Park). 2013 Sep;27(9):840, 842, 844.
6. Rubini G, Altini C, Notaristefano A, Merenda N, Rubini D, Ianora AA, Asabella AN. Role of 18F-FDG PET/CT in diagnosing peritoneal carcinomatosis in the restaging of patient with ovarian cancer as compared to contrast enhanced CT and tumor marker Ca-125. Rev Esp Med Nucl Imagen Mol. 2014 Jan-Feb;33(1):22-7.
7. Niccoli-Asabella A, Altini C, Notaristefano A, Merenda N, Altieri ML, Stabile-Ianora AA, Fanelli M, Rubini G. A retrospective study comparing contrast-enhanced computed tomography with 18F-FDG-PET/CT in the early follow-up of patients with retroperitoneal sarcomas. Nucl Med Commun. 2013 Jan;34(1):32-9.
8. Beal KP, Yeung HW, Yahalom J. FDG-PET scanning for detection and staging of extranodal marginal zone

lymphomas of the MALT type: a report of 42 cases. Ann Oncol. 2005 Mar;16(3):473-80.

9. Ferrari C, Minoia C, Asabella AN, Nicoletti A, Altini C, Antonica F, Ficco M, Guarini A, Maggialetti N, Rubini G. Whole body magnetic resonance with diffusion weighted sequence with body signal suppression compared to (18)F-FDG PET/CT in newly diagnosed lymphoma. Hell J Nucl Med. 2014 Jan-Apr;17 Suppl 1:40-9.

10. Kashyap R, Rai Mittal B, Manohar K, Balasubramanian Harisankar CN, Bhattacharya A, Singh B, Malhotra P, Varma S. Extranodal manifestations of lymphoma on [^{18}F]FDG-PET/CT: a pictorial essay. Cancer Imaging. 2011 Nov 26;11:166-74.

11. Stefanovic A, Lossos IS. Extranodal marginal zone lymphoma of the ocular adnexa. Blood. 2009 Jul 16;114(3):501-10.

12. Vollmer L. The diagnosis and management of ocular lymphoma. Optom Vis Sci. 2013 Feb;90(2):e56-62.

13. Woolf DK, Ahmed M, Plowman PN. Primary lymphoma of the ocular adnexa (orbital lymphoma) and primary intraocular lymphoma. Clin Oncol (R Coll Radiol). 2012 Jun;24(5):339-44.

14. Thieblemont C. Clinical presentation and management of marginal zone lymphomas. Hematology Am Soc Hematol Educ Program. 2005:307-13.

15. Gerami P, Wickless SC, Querfeld C, Rosen ST, Kuzel TM, Guitart J. Cutaneous involvement with marginal zone lymphoma. J Am Acad Dermatol. 2010 Jul;63(1):142-5.

16. Schöder H, Noy A, Gönen M, Weng L, Green D, Erdi YE, Larson SM, Yeung HW. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2005 Jul 20;23(21):4643-51.

17. Valenzuela AA, Allen C, Grimes D, Wong D, Sullivan TJ. Positron emission tomography in the detection and staging of ocular adnexal lymphoproliferative disease. Ophthalmology. 2006 Dec;113(12):2331-7.