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Original Article

The performance and applied value of ^{18}F-FDG PET/CT imaging in Waldenstrom macroglobulinemia

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Abstract: Waldenstrom macroglobulinemia (WM) is a rare inert B lymphocyte lymphoma and the role of FDG PET/CT imaging in WM has not been well established. This study aimed to evaluate the metabolic status of WM by ^{18}F-FDG PET/CT imaging. We retrospectively analyzed 20 patients who underwent pretherapy ^{18}F-FDG PET-CT scan. All patients were diagnosed by bone marrow aspiration, laboratory examination and clinical symptoms. Bone marrow involvement was identified with ^{18}F-FDG PET/CT imaging in 16 of 20, and the mean SUVmax of bone marrow was 4.06±0.85, Lymph nodes were involved in 8 of 20 patients, and the mean SUVmax of Lymph nodes was 4.07±1.27. Liver and spleen were involved in one case respectively, with SUVmax being 3.6 and 3.3. 1 case of extramedullary infiltration and 1 case of lymphomatous transformation. ^{18}F-FDG PET/CT imaging not only could reveal the metabolic status of lymph nodes, liver, spleen and bone marrow in WM patients, but also evaluate the status of tumor burden which helps to formulate personalized treatment plans.

Keywords: Waldenstrom macroglobulinemia, ^{18}F-FDG PET/CT, clinical characteristics

Introduction

Waldenstrom macroglobulinemia (WM) is a rare inert B lymphocyte lymphoma characterized by serum monoclonal IgM, the incidence of WM is approximately 0.38 cases per 100,000 persons per year [1-3]. The main characteristics of WM were lymphoid plasma cell infiltration in bone marrow and abnormal increase of serum monoclonal IgM. Since the incidence of the disease is low, the clinical manifestations are highly heterogeneous, and it is easy to cause missed diagnosis and misdiagnosis. Its diagnosis depends on a combination of clinical findings, serological, pathological and molecular tests. In recent years, a lot of research progress has been made on the pathogenesis and treatment of WM, especially the discovery of MYD88P.L265P mutation, which has brought substantial breakthrough for the diagnosis and treatment of WM [4-7], and IPSSWM score as a prognostic factor of overall survival (OS) and progression-free survival (PFS) for WM [8]. Although traditional imaging is not mandatory in the initial workup of a patient with WM, when extramedullary disease is present, or lymphadenopathy or organomegaly are found, then imaging examination during or after completion of therapy is advised, such as enhanced CT or MRI are required, multimodal Imaging methods can diagnose lymphoproliferative disease, determine tumor burden, identify affected sites, and thus interpret clinical manifestations, help determine prognosis and monitor treatment response [9-11]. At present, the role of FDG PET/CT imaging in WM has not been well established, with only a few published studies, and PET/CT is not a routine tool to diagnose or follow up the disease. However, PET/CT scanning is useful in the case of invasive transformation of WM because the most common histology is diffuse large B-cell lymphoma (DLBCL) [13, 14]. In recent years, with the widely use of ^{18}F-FDG PET/CT imaging in clinical practice, it can provide whole-body imaging and disease metabolic status, which is superior to traditional MR or CT imaging in determining the extent of disease. ^{18}F-FDG PET/CT imaging could afford the metabolic status of lymph nodes, spleen, liver and bone marrow, provide the extents of tumor burden in the initial status of the disease, and can also be used for disease monitor and

evaluation after treatment. In this study, we report the PET/CT findings of 20 cases of WM in order to improve the understanding of the imaging characteristics of this disease and provide diagnostic information to clinicians.

Patients and methods

Patient selection

From 2017 to 2023, 20 patients diagnosed with WM by bone marrow aspiration from the First Affiliated Hospital of USTC who underwent pre-therapy ^{18}F-FDG PET/CT examination were recruited. Any subject who has had any treatment will be excluded from this study and patients without full laboratory data were also excluded from the study. We retrospectively analyzed the metabolic characteristics of bone marrow, lymph nodes, liver and spleen of 20 patients with WM, so as to provide the initial tumor burden status and provide reference information for later clinical treatment and prognosis evaluation.

^{18}F-FDG PET/CT protocol and image analysis

All patients underwent ^{18}F-FDG PET/CT examination before treatment. ^{18}F-FDG PET/CT images were acquired using a Siemens Biograph16 PET/CT scanner (Siemens in Munich, Germany). All patients fasted for at least 6 hours before FDG PET/CT examination. At 60 minutes after intravenous injection of FDG (3.70-4.44 MBq/kg), images acquisition was started on Siemens biography 16 PET/CT scanner. PET images were acquired for 2 minutes per bed and the thickness of the attenuation-corrected CT scan was 5 mm. The CT and PET images were transmitted to the multi-slice image system for processing and analysis, so that the above two kinds of images were matched and fused frame to frame, and the axial, coronal, and sagittal CT, PET, and PET/CT fusion images were finally obtained. Two senior nuclear medicine physicians read the FDG PET/CT images independently, consensus was reached after discussion if the opinions were different. The positive criteria of bone marrow, spleen and lymph node on PET based on Deauville criteria for lymphoma. Namely, the FDG uptake at the lesion site was higher than that in the liver pool. Lymph node involvement was considered if the short diameter of lymph node was greater than 10 mm.

Laboratory examination, gene mutation test and statistical analysis

All subjects underwent serum β-2 micro-globulin and immune-electrophoresis examination, meanwhile, MYD88p.L265p mutation was also tested. SPSS22.0 software was used to analyze the correlation between PET metabolic parameters, serum IgM and β2 micro-globulin

Ethical statement

This work was approved by Institutional Review Board of the First Affiliated Hospital of USTC (2023-RE-204). The informed consent is exempted because the study was retrospective and all data was anonymous.

Results

Patient characteristics

Among a total of 20 patients, there were 16 males and 4 females, aged 43~81 years old, with an average age of 64.5±10.3 years old. Clinical manifestation included those 4 persons with reduction of the trilineage of red blood cells, white blood cells, and platelets counts during health examination; 9 patients with general fatigue; Edema of both lower limbs, spleen enlargement, multiple body mass, limb numbness, dizziness with fever, hip mass and foamy urine were recorded in 1 case each.

The characteristics of ^{18}F-FDG PET/CT images

Of the 20 cases of WM, 4 cases had negative ^{18}F-FDG PET/CT imaging and the rest showed positive ^{18}F-FDG PET imaging. The typical ^{18}F-FDG PET/CT images of WM are as follows: FDG hypermetabolism of bone marrow accompanied by FDG uptake of lymph nodes, liver or spleen (**Figure 1**); two of the WM cases showed extramedullary infiltration and lymphomatous transformation, respectively (**Figures 2**, **3**). 10 patients showed diffuse FDG uptake of bone marrow, with SUVmax values ranging from 3.6 to 6.4. 4 patients showed FDG uptake of bone marrow and lymph nodes with SUVmax values ranging from 3.5 to 5.3. 4 cases showed mild FDG uptake in spleen. 4 cases showed mild FDG uptake in the spleen with SUVmax values ranging from 3.5 to 5.3. ^{18}F-FDG PET/CT image characteristics and laboratory results of patients with WM are shown in **Table 1**.

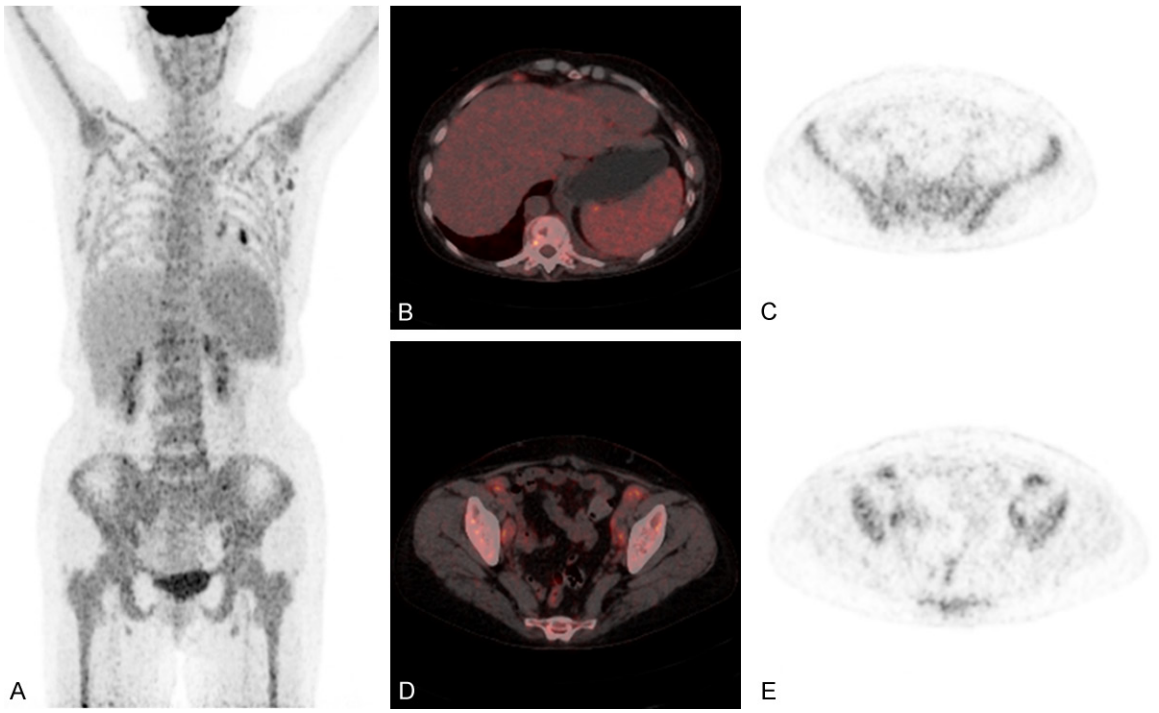

Figure 1. A systemic skeletal increased FDG uptake was seen on PET MIP image (A). Mild liver enlargement and mild FDG uptake of spleen were observed on transverse PET and fusion PET/CT images (B). Moderately increased FDG uptake in the sacrum and bilateral iliac crest, as shown in cross-sectional PET images (C). Bilateral para-iliac lymphatic enlargement with mild FDG uptake was showed on transection fusion PET/CT and PET image (D and E).

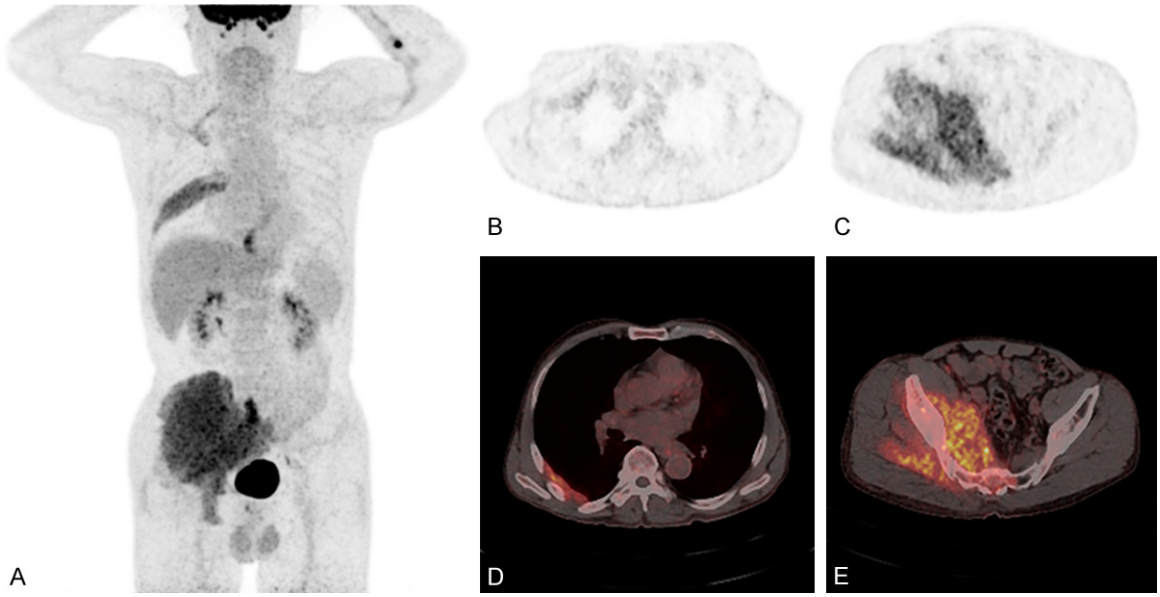

Figure 2. Striped and lumpy FDG uptake were seen in the right chest and right pelvis on PET MIP image (A). The strip mild FDG uptake was seen in the right first anterior rib with SUVmax being 2.5 (B). Diffuse FDG uptake was seen in the right pubococcygeus, gluteus medius and minimus, ilium and sacrum on cross-sectional PET and fused PET/CT images, with SUVmax being 6.1 (C and E). Striped FDG uptake in the right pleura was seen in on axial PET/CT fusion images (D).

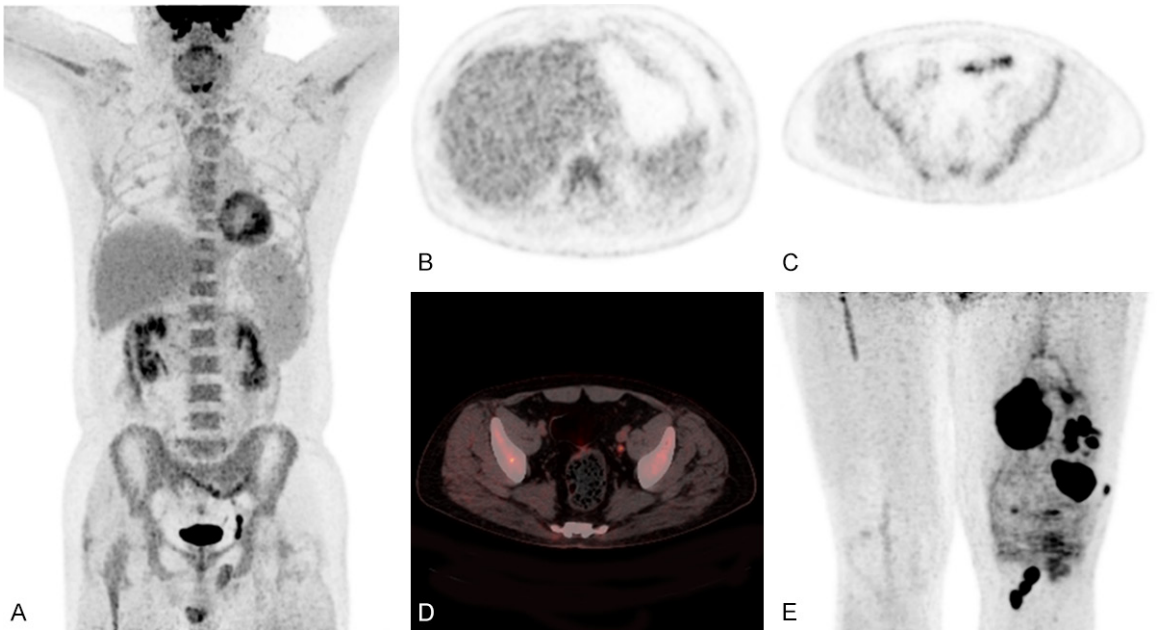

Figure 3. Diffuse inhomogeneous FDG uptake in whole-body bone on PET MIP image (A). Mildly elevated radioactivity uptake in the liver and spleen on cross-sectional PET images with SUVmax being 2.6 (B). Diffuse FDG uptake in bilateral iliac bones with SUVmax being 3.3 (C). Left external iliac paravascular lymph node FDG uptake with SUVmax being 4.0 (D). Multiple nodular FDG uptake were seen in the left lower extremity muscle interstitium with a SUVmax of 12.7 and biopsy pathology of diffuse large B-cell lymphoma (E).

Laboratory examination and gene mutation test result

Serum IgM values ranged from 6.10 g/L to 117.17 g/L, the maximum value of IgM was 117.17 g/L, the minimum value was 6.10 g/L, and the average value was 36.61±29.66 g/L; The serum concentration of β2 microglobulin ranged from 1.97 mg/L to 23.50 mg/L, with a maximum of 23.5 mg/L and a minimum of 1.97 mg/L, and a mean of 6.32±4.90 mg/L; Of the 20 Waldenström macroglobulinemia patients, 17 had MYD88 mutations and 3 are MYD88 wild-type.

Statistical analysis result

The results of SPSS22.0 statistical analysis show that no correlation between IgM and uptake of FDG SUVmax in bone marrow, liver, spleen and lymph nodes. Meanwhile, the correlation between the maximum value of SUVmax and serum IgM and β2 microglobulin was also analyzed, and no correlation among them was found. The bone marrow uptake values were standardized and a statistical analysis was performed, a moderately to weak correlation result between β2 microglobulin and the ratio of bone marrow SUVmax to liver SUVmax was obtained (r=0.48, P=0.03).

Discussion

The diagnostic key factor of WM consists of three points, including that Monoclonal IgM immunoglobulin was present in serum; typical lymphoplasmacytic cells can be seen in the bone marrow, and whether there are related clinical symptoms. The diagnosis was IgM MGUS (monoclonal gammopathy of undetermined significance MGUS) when only serum monoclonal IgM was present [15]. If the first two items are met, the diagnosis is asymptomatic or smoldering WM, and symptomatic WM was diagnosed only when all 3 criteria were met. The World Health Organization defines the diagnosis of WM as: histopathology lymphoplasmacytic/lymphoplasmacytic lymphoma (LPL) has been identified in bone medullary infiltration and any amount of monoclonal immunoglobulin M detected (IgM) [16-18]. The confirmation of these two points should be combined with pathological and immunophenotyping, molecular genetics and clinical manifestations. In addition to laboratory tests, imaging also plays an auxiliary value in the diagnosis

Table 1. Clinical manifestation, biological features, and ^{18}F-FDG PET/CT metabolic parameters of WM

Patient	Sex/age	M-protein type	IgM (g/L)	β2-MG (mg/L)	Involvement site	MYD88	Bone marrow (SUVmax)	Lymph node (SUVmax)	Liver (SUVmax)	Spleen (SUVmax)	Mediastinum (SUVmax)
1	F/61	IgM_k	25.20	7.46	BM, LN, SP	positive	6.4	3.2	3.5	3.6	2.5
2	M/59	IgM_k	21.30	1.97	BM, LN	positive	3.7	5.2	3.3	2.8	1.6
3	M/67	IgM_k	17.60	6.36	BM, LN	positive	3.9	2.0	2.8	2.6	1.8
4	M/68	IgM_k	21.30	5.30	BM, SP	positive	4.2	1.8	2.8	2.8	1.7
5	M/43	IgM_k	117.17	3.1	SP	negative	2.2	1.5	2.9	3.3	2.1
6	M/74	IgM_L	19.80	8.54	Liver	positive	1.7	1.7	4.5	2.6	1.4
7	F/74	IgM_L	6.10	4.27	BM	positive	2.8	1.0	3.8	3.3	2.4
8	M/51	IgM_k	74.10	5.03	BM, LN	positive	4.3	5.3	3.2	2.3	2.2
9	M/59	IgM_k	20.40	7.45	BM	positive	3.9	1.0	2.4	2.4	1.6
10	M/71	IgM_k	36.45	4.45	SP	positive	2.4	1.5	3.3	3.5	2.3
11	M/62	IgM_L	7.15	2.24	Liver, SP	negative	2.5	2.0	3.6	2.9	2.2
12	M/81	IgM_k	63.70	7.48	BM, SP	positive	4.8	2.7	2.6	2.6	1.6
13	M/73	IgM_L	29.0	8.07	BM, LN	positive	3.5	4.5	2.4	2.0	1.3
14	M/67	IgM_k	67.80	23.50	BM	positive	4.2	2.5	3.0	2.6	1.8
15	M/72	IgM_k	56.90	3.55	BM	positive	3.7	1.1	3.2	2.8	1.8
16	M/57	IgM_L	26.07	2.65	BM	positive	3.6	1.4	2.5	2.8	1.8
17	F/59	IgM_k	12.41	6.05	BM, SP, LN	positive	3.8	4.2	2.3	3.3	1.3
18	F/77	IgMk	34.66	6.05	BM, LN	negative	2.8	3.2	2.3	1.9	1.5
19	M/66	IgML	9.58	2.56	BM, Muscle, pleura	positive	3.3	4.0	3.0	2.6	1.8
20	M/47	IgML	9.82	3.89	BM, LN, Muscle space	positive	2.9	2.2	2.7	1.9	1.8

and staging of WM. However, there have been few studies on the imaging manifestations of WM, which may be due to the lack of imaging characteristics or low incidence of this disease. Imaging methods are mostly used to evaluate extent of disease involvement after diagnosis of WM. Therefore, MRI and CT can be used as adjuvant staging and post-treatment evaluation of WM [19].

On ^{18}F-FDG PET/CT baseline scanning, the positive scan of WM ranged 20% to 77% according to literature reports [20, 21]. WM positive PET/CT imaging rate was 80% (16/20) and the bone marrow 75% (15/20) is the most affected sites in our studies, which was similar to that reported in the literature, the reason for negative PET/CT imaging due to the WM was indolent lymphoma, and indicates that the negative cases may be smoldering WM. The positive PET/CT imaging of bone marrow, lymph nodes, liver and spleen indicated that the metabolic activity of the lesion was increased, suggesting the need for clinical treatment of the disease. The cases in our study were mostly older men, with an average age of over 54 years old and a male to female ratio of about 4:1. WM mostly presents diffuse increased FDG uptake of bone marrow, which is higher than the FDG uptake of liver blood pool. However, bone destruction rarely occurs, accounting for approximately 1.75% of WM patients, when bone destruction occurs in these rare cases, which is easily misdiagnosed as multiple myeloma [22-24]. For ^{18}F-FDG PET/CT imaging negative or not ideal cases, ^{68}Ga-Pentixafor PET/CT imaging can be supplemented for evaluation of WM [25, 26], and ^{64}Cu-AMD3100 PET imaging might be potential technology to detect hypoxic-metastatic WM cells in the bone marrow [27]. Through statistically analyzed for laboratory data and PET/CT parameters, we found that laboratory β2 microglobulin had a moderately to weak correlation with the ratio of bone marrow SUVmax to liver SUVmax, whereas laboratory β2 microglobulin has been reported in the literature to be a prognostic indicator for WM [28], so the ratio of bone marrow SUVmax to liver SUVmax may be a prognostic indicator for WM. An important manifestation of poor prognosis of WM is the conversion to lymphoma, which can be clinically monitored by the elevated serum lactate dehydrogenase (2 points), platelet count $<100\times10^9$/L (1 point), and any previous treatment for WM (1 point) [29-31], ^{18}F-FDG PET/CT imaging can be useful in cases of aggressive transformation of WM, the higher FDG SUVmax of the lesions may be a predictor of WM conversion to lymphoma, and only 1 (5%) case conversion to lymphoma was found in our study. Extramedullary infiltration is another factor in the poor prognosis of WM, and 1 (5%) case in our small sample study had pleural and muscle invasion, which was well demonstrated and evaluated by ^{18}F-FDG PET imaging. The series of our study was small, and all image features of WM were not fully included. Especially, extramedullary organ involvement is not fully covered, so there may be some bias in the final conclusion. We are looking forward to prospective studies with larger samples in the future.

Conclusion

In conclusion, the feature of WW on ^{18}F-FDG PET/CT is characterized by abnormally hypermetabolism of bone marrow, which may be accompanied by FDG high uptake of lymph nodes and/or spleen, and some cases may be negative. Extramedullary infiltration and malignant lymphoma transformation occur in very few cases. ^{18}F-FDG PET/CT imaging could evaluate the metabolic status and tumor load of bone marrow, liver, spleen and lymph nodes in initial diagnosed WM. Simultaneously, it can also monitor extramedullary infiltration and lymphoma transformation. In addition, the ratio of bone marrow SUVmax to liver SUVmax may be a prognostic indicator for WM. Therefore, whole-body ^{18}F-FDG PET/CT imaging could provide auxiliary information for the diagnosis, treatment, and prognosis of this disease.

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Disclosure of conflict of interest

None.

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