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Scientific Research

Findings of ^{18}F-Fluorodeoxyglucose Positron-Emission Tomography in Methotrexate-Related Lymphoproliferative Disorder

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Abstract

Introduction: The use of methotrexate (MTX) for rheumatoid arthritis (RA) is increasing. However, the immune suppression state leads to the occurrence of lymphoproliferative disorder (MTX-LPD). The purpose of this study was to describe the findings of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in MTX-LPD patients, and compare it with non-MTX-related malignant lymphoma (ML). Materials and Methods: We retrospectively reviewed 11 MTX-LPD patients (9 female, mean age 68.3 years) and 21 ML patients (7 female, mean age 60.6 years) with a histopathological diagnosis. FDG-PET imaging was performed using a standard oncology procedure. We assessed the disease distribution based on FDG-PET images and measured the maximum standardized up take values (SUVmax) for each region. Results: Mean values of SUVmax in MTX-LPD and ML were 14.6 and 17.2, respectively ($p = 0.49$). In MTX-LPD, 55 lesions met the Cotswold classification, consisting of 37 nodal and 18 extranodal lesions. In ML, 82 lesions were found, consisting of 68 nodal and 14 extranodal lesions. MTX-LPD showed a higher incident of the involvement in extranodal lesions throughout the whole body ($p < 0.001$). Conclusion: Because this disease occurs widely throughout the whole body, we need to pay attention to the less frequent sites as well when performing PET imaging in patients with MTX-LPD.

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Keywords

Fluorodeoxyglucose (FDG) F 18, Lymphoma, Methotrexate, Positron-Emission Tomography (PET), Rheumatoid Arthritis

1. Introduction

Methotrexate-related lymphoproliferative disorder (MTX-LPD) is a rare disease. It was first reported in 1991 [1] and is now recognized by the World Health Organization [2]. It is known as a treatment-related disorder that arises in patients with rheumatoid arthritis (RA). Methotrexate (MTX) is now widely used in RA patients because it has an immunosuppressive effect that reduces joint inflammation. Therefore, MTX has become a necessary and core component in the treatment of RA. However, the background immune abnormality in RA and the use of MTX as an immunosuppressive drug has been considered one of causes for MTX-LPD [3].

The characteristics of MTX-LPD can be summarized as follows [4]-[6]: 1) it occurs in old age, and in patients with a relatively long history of RA, following a treatment period with MTX of about 30 - 50 months and with a cumulative dose of MTX of 1500 mg; 2) it is associated with infection with Epstein-Barr virus (EBV); 3) it shows a predominance with diffuse large B-cell lymphoma (DLBCL); 4) it shows no predominance between nodal and extranodal lesions; 5) it can regress following withdrawal of MTX.

Recently, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging has been widely adopted for the diagnosis and management of patients with malignant tumors. The high diagnostic performance of FDG-PET [7] also makes this modality the current first choice for diagnosis of patients with lymphoma. However, the use of FDG-PET for diagnosis of MTX-LPD has not been widely reported in the existing literature [6] [8]-[10]. The purpose of this study is to describe the findings of FDG-PET imaging as well as characteristics of patients with MTX-LPD.

2. Materials and Methods

The institutional review board (IRB) approved this retrospective study and waived the requirement for written informed consent.

We searched the medical records in the division of medical oncology/hematology and a PET database in the division of radiology for patients with MTX-LPD. Patients diagnosed with MTX-LPD with histological proof who had undergone a FDG-PET scan were consecutively reviewed. We selected malignant lymphoma (ML) patients as a control group from a PET database during the same period, as we matched patients according to the pathological subtypes as much as possible. ML patients were also proven with a pathological examination, and had no history of RA and treatment with MTX.

We analyzed the findings of FDG-PET images with reading of a radiologist with a board certification of nuclear medicine. The distribution of the disease was analyzed visually and classified according to the Cotswold classification [11]. The maximum value of SUV (SUVmax) of the disease was measured for the region showing the highest uptake of FDG in the body.

2.1. Image Acquisition

The FDG-PET scan was performed using a standard protocol for cancer evaluation. We performed PET or PET-CT imaging according to the standard clinical schedule. After at least 6 h of fasting, patients received an intravenous injection of 222 - 333 MBq (6 - 9 mCi) of ^{18}F-FDG and images were obtained 60 minutes later. The blood glucose levels were checked in all patients before FDG injection, and no patients showed a blood glucose level of more than 160 mg/dL.

PET imaging was performed using a Philips Allegro instrument (Philips Medical Systems, the Netherlands). The patients were positioned and a static emission scan was performed with 2.5 - 3 minutes of acquisition in each bed position. The PET component of the combined imaging system allowed simultaneous acquisition of 45 transaxial images at 4 mm intervals, and provided an image from the meatus of the ear to the mid-thigh with 9 - 10 bed positions. A transmission scan using a ^{137}Cs ring was then performed over the same area with a transmis-

sion scan of 23 seconds per bed position. PET images were reconstructed using an ordered-subset expectation maximization iterative reconstruction algorithm.

PET/CT imaging was performed using a Discovery PET/CT 690 instrument (GE Healthcare, USA). A preliminary low-dose CT scan was acquired and used for attenuation correction and image fusion. The CT covered a region ranging from the meatus of the ear to the mid-thigh. The PET component of the combined imaging system allowed simultaneous acquisition of 47 transaxial PET images with an interslice spacing of 3.27 mm in one bed position, and provided an image from the meatus of the ear to the mid-thigh with 7 - 8 bed positions. Emission images were acquired in 3-dimensional acquisition mode for 2 minutes per bed position. Attenuation-corrected PET images were reconstructed with an ordered-subset expectation maximization iterative reconstruction algorithm (18 subsets, 2 iterations).

2.2. Statistical Analysis

Continuous values are expressed as mean, and categorical values as absolute values. For categorical values, Fisher's exact test was performed. For continuous values, unpaired *t* test was performed. A p value of <0.05 was considered statistically significant.

3. Results

A total of 11 MTX-LPD patients and 21 ML patients were reviewed from June 2007 to June 2013. Patient characteristics are summarized in **Table 1**. In MTX-LPD group, the mean age was 68.5 years (range: 57 - 75 years). Nine female and 2 male patients were included. The mean period from the introduction of MTX was 60.0 months (range: 18 - 125 months). The mean dose of MTX at the diagnosis was 8.38 mg/week (range: 6 - 15 mg). The mean value of sIL-2R was 2607 U/ml (range: 475 - 12653 U/ml), and the mean value of lactate dehydrogenase was 267.3 IU/I/37˚C (range: 176 - 449). Pathological inspection was consistent with the following findings: diffuse large B-cell lymphoma (DLBCL) (n = 6), Hodgkin lymphoma (n = 3), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type (MALT) (n = 1), and peripheral T-cell lymphoma (n = 1). In ML group, the mean age was 60.6 years (range: 13 - 82 years). Seven female and 14 male were included. They were consisted of 12 DLBCL, 5 Hodgkin lymphoma, 2 MALT, and 2 peripheral T-cell lymphoma.

Table 1. Summary of patient characteristics.

	MTX-LPD	ML	p value
	n = 11	n = 21	
Mean age (y)	68.5 (57 - 75)	60.6 (13 - 82)	0.21
Gender (female:male)	9:2	7:14	0.02
Mean period from the introduction of MTX (mo)	60.0 (18 - 125)	-	-
Mean dose of MTX at the diagnosis (mg/week)	8.38 (6 - 15)	-	-
Mean sIL-2R value (U/ml)	2607 (475 - 12653)	1362 (217 - 6887)	0.20
Mean value of lactate dehydrogenase (IU/I/37˚C)	267.3 (176 - 449)	303.0 (152 - 1128)	0.66
Pathology			1.0
DLBCL	6 (54.5%)	12 (57.1%)	
Hodgkin	3 (27.3%)	5 (23.8%)	
MALT	1 (9.1%)	2 (9.5%)	
PTCL	1 (9.1%)	2 (9.5%)	
Mean blood glucose at PET scan (mg/dl)	85.9 (71 - 99)	89.4 (62 - 177)	0.64
Mean SUVmax	14.6 (3.6 - 32.8)	17.2 (5.3 - 39.5)	0.49
Presence of nodal lesion (n)	8 (72.7%)	20 (95.2%)	0.11
Presence of extranodal lesion (n)	11 (100%)	7 (33.3%)	<0.001

Data are expressed as mean (range) or absolute value (percentage). MTX: methotrexate; ML: malignant lymphoma; sIL-2R: serum interleukin-2 receptor; DLBCL: diffuse large B-cell lymphoma; MALT: marginal zone lymphoma of mucosa-associated lymphoid tissue type; PTCL: peripheral T-cell lymphoma; SUVmax: maximum standard uptake value.

Representative cases of MTX-LPD are shown in **Figure 1** and **Figure 2**. The distribution of the lesions is summarized in **Table 2**. The details of MTX-LPD patient characteristics and PET findings are listed in **Table 3**. A total of 55 lesions were observed in MTX-LPD, including 37 nodal and 18 extranodal lesions. The mean SUVmax was 14.6 (range: 3.6 - 32.8). On the other hand, 82 lesions were observed in ML, including 68 nodal and 14 extranodal lesions, with the mean SUVmax of 17.2 (range: 5.3 - 39.5). The value of blood glucose level was not different between the groups.

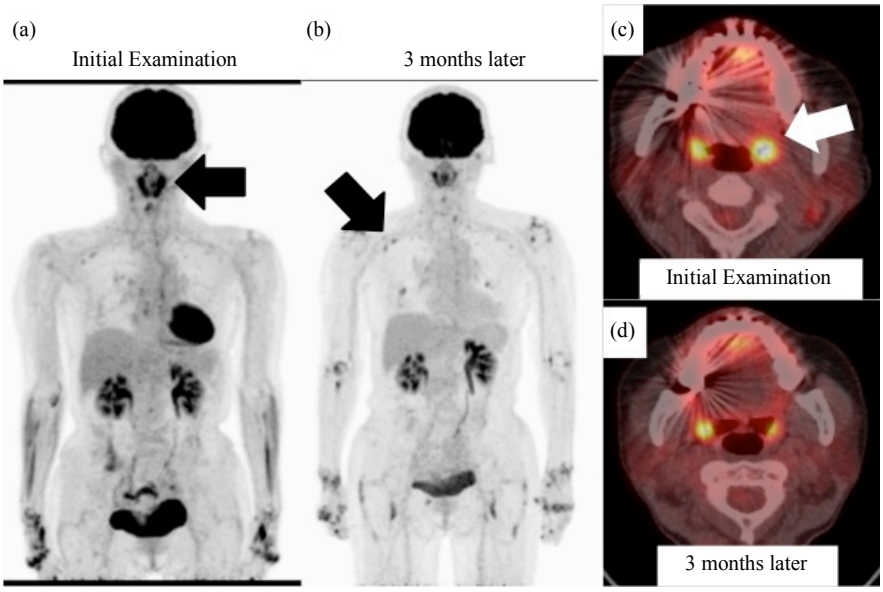

Figure 1. A 75-year-old lymphoproliferative disorder female with a use of MTX for 30 months. Bilateral tonsils show high accumulation of FDG on initial examination ((a) black arrow; (c) white arrow). The biopsy from the tonsils revealed diffuse large B cell lymphoma. However, these accumulations decreased 3 months after the withdrawal of MTX (b) and (d). On the other hand, the accumulation in the joints such as shoulders, elbows, wrists are worsened (b). Although the accumulation in axilla lymph nodes is also seen ((b) black arrow), it is considered to be reactive accumulation because the accumulation worsens slightly and is not coincident with the improvement of the tonsil disease.

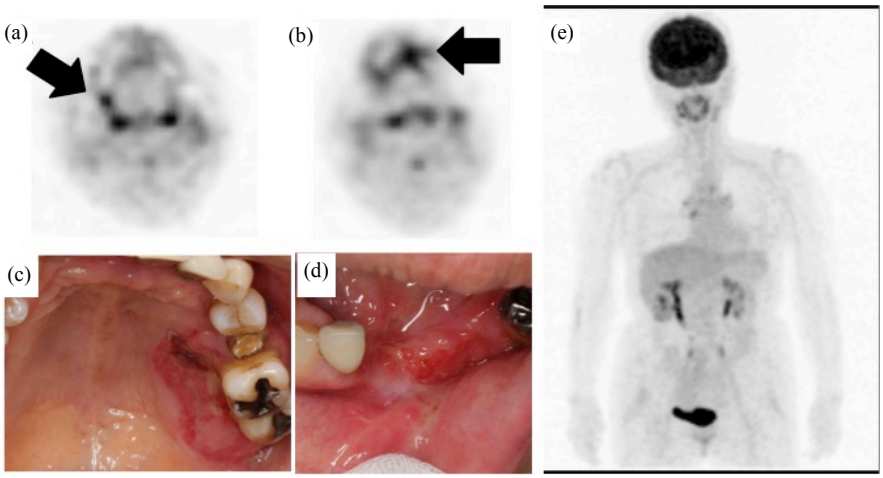

Figure 2. A 64-year-old lymphoproliferative disorder female with a use of MTX for 56 months Accumulation of the gingiva ((a) and (b) black arrow) is shown. There are two ulcers, one is in the left upper gingiva (c) and the other is in the back of the lower lip (d); these are coincident with the PET images, and were pathologically diagnosed as diffuse large B cell lymphoma. No other abnormal accumulation occurred in the body (e).

Table 2. Summary of the distribution of the lesions of methotrexate-related lymphoproliferative disorder (MTX-LPD) and malignant lymphoma (ML).

	Region	MTX-LPD	ML
		n = 55	n = 82
Nodal	Waldeyer's ring	3	8
	Neck LN	6	13
	Mediastinum LN	4	8
	Subclavicular LN	2	7
	Axilla LN	4	6
	Hilar LN	4	3
	Para abdominal aortic LN	2	8
	Spleen	3	5
	Mesenteric LN	3	2
	Pelvic LN	3	4
	Inguinal LN	3	4
Extranodal	Parotid gland	1	0
	Gingiva	2	0
	Lung	1	0
	Bone	6	4
	Skin	2	3
	Orbit	1	2
	Pleura	2	1
	Nasal cavity	1	0
	Heart	1	1
	Muscle	1	1
	Liver	0	2

LN: lymph node.

Table 3. Clinical data of patients with methotrexate-related lymphoproliferative disorder.

Case	Age and Gender	Time	Dose	Pathology	sIL-2R	SUVmax	Lesions	
	(y)	(mo)	(mg/week)		(U/ml)		Nodal	Extranodal
1	57F	54	NA	MALT	894	3.6	0	1
2	74F	120	6	DLBCL	918	21.2	1	6
3	75F	63	8.75	Hodgkin	1942	10.6	2	1
4	69M	81	15	DLBCL	1170	31.3	0	1
5	71F	70	6	DLBCL	889	12.2	4	2
6	69F	59	8	Hodgkin	4911	14.8	10	1
7	72F	84	8	PTCL	1498	7.6	4	1
8	67F	25	8	Hodgkin	12653	11.8	9	1
9	64F	56	6	DLBCL	1041	4.2	0	1
10	75F	30	6	DLBCL	475	10.3	3	1
11	61M	18	12	DLBCL	2283	32.8	4	2

Time: time from the introduction of methotrexate (MTX); Dose: dose of MTX at the diagnosis; sIL-2R: serum interleukin-2 receptor; SUVmax: maximum standard uptake value; MALT: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type; DLBCL: diffuse large B-cell lymphoma; PTCL; peripheral T-cell lymphoma.

MTX-LPD showed a higher incidence of the extranodal involvement compared to ML ($p < 0.001$); however, the incidence of nodal lesions was not different ($p = 0.11$) (**Table 1**).

4. Discussion

The conventional treatment of RA combines corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs). Recently, MTX has become one of the central drugs of the treatment, and is recommended as a first-line drug by the European League Against Rheumatism (EULAR) [12] and the American College of Rheumatology (ACR) [13]. Despite the usefulness of MTX, a relationship between MTX treatment and the occurrence of lymphoproliferative disorders (LPD) has been topic of discussion for many years [5] [14] [15]. The combination of the RA-related oncogenicity, MTX-related immune-suppression, and EBV-related oncogenicity is now considered a cause of MTX-LPD.

In this study, MTX-LPD showed a female predominance, mainly due to the female dominance of RA, and a mean age of 68.5 years; these results were compatible with previous reports [5]. The mean period from the introduction of MTX was 60 months; however, two patients had taken MTX for less than 30 months. This period was compatible with the approximately 50 months previously reported [5]. In addition, our series also showed DLBCL predominance (54.5%, 6/11), which was also compatible with previous reports [3] [5]. MTX are also used in the patients with autoimmune diseases such as systemic lupus erythematosus. However, there is no report consisting of a large number of autoimmune diseased MTX-LPD or its FDG-PET finding.

MTX-LPD showed a wide distribution throughout the entire body according to PET findings. Compared to general ML, MTX-LPD showed a significantly high incidence of the extranodal involvement. The extranodal lesions frequently involved the bone. Only one case showed primary bone lymphoma, while the other 5 cases were associated with advanced lymphoma. Less frequent sites were also observed. First, our series showed a pericardial involvement ($n = 1$), a lung nodule ($n = 1$) and pleural involvement ($n = 2$) although intra-thoracic involvement is more common in Hodgkin disease than in NHL [16] [17]. Second, the gingiva was involved in two cases, where one showed ulcers in the gingiva and disease only in the oral cavity as we presented in **Figure 2**. Kikuchi *et al*. suggested that oral bacteria had some effect on the occurrence of MTX-LPD [18]. Third, the skin was involved in 2 cases in our series. Georgescu *et al*. found 2 patients with skin involvement in 25 MTX-LPD patients [3]. Although FDG-PET is useful in the diagnosis of skin lymphoma [19], it could be difficult to diagnose in the early stages, especially if PET-CT is not used. Fourth, in our series, one case involved the muscle with a relatively advanced stage. Primary skeletal muscle lymphoma is very rare and the majority of the muscle involvement occurs by means of dissemination from nodal disease [17]. As above, we have to keep in mind the rare sites of MTX-LPD involvement, and should pay attention to the whole body.

The mean value of SUVmax in MTX-LPD was 14.6 (range: 3.6 - 32.8). This was not significantly different from pathological subtype-matched ML group with mean SUV of 17.2 ($p = 0.49$). Schoder *et al*. reported a difference in the uptake of FDG according to the subtype of ordinary lymphoma [20]. In addition, the uptake of FDG is determined by many factors: histologic features, grade, viable tumor cell fraction, tumor cell proliferation, glucose metabolism, local perfusion, and hypoxia [17]. Indolent lymphoma such as follicular lymphoma is well known to have a lower uptake. We should take care when considering cases showing low uptake in FDG-PET with lymphadenopathy under MTX treatment.

FDG-PET is used for the evaluation of the treatment of lymphoma [21]. Therefore, it is expected to monitor the disease activity and response to treatment in MTX-LPD patients as well. The initial treatment for MTX-LPD is withdrawal of MTX [22]. The lesions are expected to diminish after MTX is withdrawn; however, the interval of the remission after the withdrawal is not clear. In addition, as we presented in Figure 1, the inflammation of the joints will be worsened after the withdrawal of MTX, thereby increasing the accumulation in the axilla or inguinal LN. Although this is considered reactive accumulation, the differentiation between reactive accumulation and a relapse of MTX-LPD would be difficult and problematic. We should consider the disease activity with other clinical information such as the value of sIL-2R. Further examination is needed to establish the optimal interval and usefulness of the PET image for treatment monitoring.

This study had several limitations. The number of the patients examined in this study was relatively small, mainly because MTX-LPD is a rare disease. In addition, some cases of MTX-LPD showed histologically aggressive types of lymphoma and did not undergo FDG-PET in this study because the PET schedule was crowded; these patients were treated after whole body CT scans. We did not necessarily obtain the pathological proof

from all lesions. Because MTX-LPD is a systemic disorder, performing biopsy from all lesions is not realistic. Thus, the reference standard was missed and the distribution was based on the reading of an experienced radiologist. Moreover, the low uptake lymphoma might be missed because we focused on the high uptake lesions. The contrast enhanced CT or MRI will be needed to detect the lymphoma with low uptake of FDG. EBV is an oncogenic virus, and persistent infection exists in 90% of adult humans. The immunosuppressive state resulting from MTX treatment reactivates EBV, causing the development of ML [23] [24]. We did not include the analysis of EBV infection in this study. We also have no accurate data on the total doses of MTX because some patients had a long history of RA, and their dosages were changed during that period. We did not perform a follow-up study using FDG-PET because of this was a retrospective study. We believe that FDG-PET has the potential to monitor the disease activity or the treatment effectiveness, although further examination is needed to confirm this point.

5. Conclusion

MTX-LPD shows a wide distribution in the body according to the FDG-PET findings. Because this disease occurs widely throughout the whole body, we need to pay attention to the less frequent sites as well when performing PET imaging in patients with MTX-LPD.

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