

## Diagnostic relevance of 18F-FDG PET/CT in newly diagnosed patients with monoclonal gammopathy of undetermined significance (MGUS): Single-center experience

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Received November 4, 2019 / Accepted February 6, 2020

Monoclonal gammopathy of undetermined significance (MGUS) is a known precursor of more serious cancers, such as multiple myeloma (MM), Waldenström macroglobulinemia (MW) and other lymphoproliferative disorders. Using 18F-FDG PET/CT, we aimed to evaluate its benefit in early detection of various accompanying disorders and illnesses in MGUS patients. We prospectively analyzed the diagnostic relevance of 18F-FDG PET/CT in 390 newly diagnosed MGUS patients. On 18F-FDG PET/CT scans, the presence of focal or diffuse areas of detectable increased tracer uptake was recorded in 37 (9.5%) MGUS patients. The most frequent pathology was lymphadenopathy (3.8%), followed by thyroid diseases (2.1%), rheumatic diseases (1.8%), and other solid malignancies (1.5%). These results have major implications for confirmed associations of MGUS with numerous malignant and non-malignant disorders. We believe that 18F-FDG PET/CT imaging in newly diagnosed MGUS patients may be useful in early detection of other serious pathologies, not only in predicting progression of MGUS to active MM, and should be strongly recommended if available.

*Key words: monoclonal gammopathy, cancer, multiple myeloma, PET/CT*

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common pre-malignant disorders and affects approximately 3.5% of the population over 50 years of age [1, 2]. IgG and IgA isotypes MGUS are defined by serum monoclonal immunoglobulin (M-protein) <30 g/l in serum, bone marrow (BM) plasma cell percentage <10%, and absence of signs or symptoms related to multiple myeloma (MM) (CRAB criteria: hypercalcemia, renal insufficiency, anemia, or bone lesions) or other lymphoproliferative disorders [3]. IgM isotype MGUS is defined by serum IgM M-protein less than 30 g/l, bone marrow lymphoplasmacytic infiltration <10%, and absence of end-organ damage. Light-chain MGUS is defined by an abnormal  $\kappa/\lambda$  free light-chain (FLC) ratio, an increase in the concentration of the involved light chain, and absence of expression of a monoclonal peak of immunoglobulin heavy chain in serum on immunofixation [3]. IgG or IgA MGUS patients typically progress to MM, and IgM MGUS patients typically develop into Waldenström macroglobulinemia (MW) or other lymphoproliferative disorders [4]. Patients with a light chain only asymp-

tomatic monoclonal gammopathy are at risk of developing light-chain MM or immunoglobulin light-chain amyloidosis (AL amyloidosis) [1, 5, 6]. Progression of MGUS to MM or other related malignancies occurs at a rate of approximately 1% per year [7–10]. Furthermore, MGUS patients have an approximately 2–8-fold increased risk of developing myeloid malignancies, including myelodysplastic syndrome (MDS), acute myeloid leukemia, and polycythemia vera [11, 12] and an approximately 1.5-fold increased risk of developing a non-hematologic malignancy [11–13].

Among newer imaging techniques, positron emission tomography (PET) integrated with computed tomography (PET/CT) using glucose labeled with the positron-emitting radionuclide 18F (fluorodeoxyglucose (18F-FDG)) is a standard technique in the diagnosis and management of serious illnesses, several types of tumors and for FDG-avid lymphomas, it is crucial for staging and treatment response [14–16]. Furthermore, it is a reliable technique for assessing early skeletal involvement and for predicting outcomes at the onset of MM [17–20]. The International Myeloma Working

Group (IMWG) consensus aimed to provide recommendations for the optimal use of PET/CT in MM patients and other plasma cell disorders, including smoldering multiple myeloma (SMM) and solitary plasmacytoma [21]. Nevertheless, data for the role of PET/CT in diagnostic relevance in MGUS patients are still limited.

Since MGUS patients have an increased risk of developing hematologic and non-hematologic malignancies, we performed PET/CT imaging in all newly diagnosed MGUS patients. Our data show that using PET/CT imaging in newly diagnosed MGUS patients may be useful for the early detection of various malignant and non-malignant disorders, not only for verification of CRAB symptoms. According to our knowledge, this is the first recommendation for the use of PET/CT imaging in MGUS patients.

## Patients and methods

**Patient selection.** In total, 390 consecutively diagnosed MGUS patients were enrolled in a prospective clinical imaging study. Patients presenting with underlying osteolytic lesions and/or paramedullary lesions, arising from bone, and/or extra-medullary disease, arising in soft tissues, were excluded from the study as they were considered to have active MM, according to the new diagnostic criteria [3]. At the time of PET/CT imaging, these patients showed no specific symptoms indicative of later diagnosed illnesses. All MGUS patients were diagnosed and monitored at the Department of Internal Medicine, Hematology and Oncology at the University Hospital Brno, Czech Republic, from January 2010 to December 2016. The diagnosis of MGUS was made according to the updated 2010 IMWG diagnostic criteria [22]. Written informed consent approved by the Ethics committee of the hospital was obtained from all patients before enrollment of the study in accordance with the current version of the Helsinki declaration. Imaging scans were reviewed by a radiologist and a nuclear medicine physician. The baseline characteristics of the entire patient group are listed in Table 1. The median age of all patients was 63 years (range 22–93 years), and there were equal numbers of males and females. Only 15.4% (60/390) patients were younger than 50. The predominant monoclonal isotype was IgG, which occurred in 69.6% (271/390) of patients. Overall 12.4% (48/390) of patients had an M-protein value  $\geq 1.5$  g/dl at diagnosis. The abnormal value of FLC ratio ( $\kappa$  to  $\lambda$  ratio  $< 0.26$  or  $> 1.65$ ) was detected in 43.4% (169/390) of patients. Immunoparesis was detected in 25.2% (98/390) of patients.

**Laboratory evaluation.** All patients underwent myeloma specific tests, including serum and urine immunofixation electrophoresis, serum free light chain assay, serum immunoglobulin, serum beta-2-microglobulin, and lactate dehydrogenase. Bone marrow aspirates and biopsies were obtained for cytological and histopathological evaluation of plasma cell infiltration. Clonality assessment and aberrant plasma cell percentage was determined in bone marrow aspirate by

8 color flow cytometry using European Myeloma Network Gating criteria [23]. Immunoparesis was defined as one or more immunoglobulins less than the lower limit normal for our laboratory's respective reference range (IgA  $< 0.61$  g/l, IgG  $< 7.67$  g/l, IgM  $< 0.5$  g/l). FLC estimation was carried out using serum FLC assay (FreeliteH, The Binding Site Limited, Birmingham, UK) performed on a Dade Behring Nephelometer (Deerfield, IL, USA) [24]. A complete radiological examination of the skeleton was performed in all patients to exclude osteolytic lesions.

**18F-FDG PET/CT technique.** Patients underwent whole body PET/CT imaging within 6 months of MGUS diagnosis, performed at the Department of Nuclear Medicine, Masaryk Memorial Cancer Institute, Brno, Czech Republic; images were thereafter uploaded in a system for central review. PET/CT scans were acquired according to a local protocol (applying EANM (European Association of Nuclear Medicine) PET procedure guidelines for FDG studies) [25]. All patients had standard preparation prior to the examination, including restriction of physical activity for 12 h, fasting for at least 6 h, capillary glycemia below 10 mmol/l (180 mg/dl) prior to 18F-FDG administration and peroral hydration with 500–1,000 ml of plain water. 18F-FDG was administered in a dose of 3.5–4.5 MBq/kg. After an *in vivo* accumulation time of 55 to 90 minutes, whole body scanning including the tip of the skull to the lower third of the femoral shafts and the upper limb (total body range) were performed. PET/CT examination was performed utilizing the hybrid scanner Biograph 64 HR+Siemens Erlangen, Germany. All images were iteratively reconstructed and corrected for attenuation. 18F-FDG uptake was assessed visually and also semi-quantitatively in the defined region of interest (ROI) with the calculation of target-to-liver ratios. Liver 18F-FDG uptake (SUV<sub>max</sub>) was used as a reference base (measured within the ROI located in the centrum of the right liver lobe). A target-to-liver ratio  $> 1.0$  was considered positive in all mentioned regions.

## Results

In total, 390 newly diagnosed MGUS patients were evaluated; these patients did not have any lytic lesions on skeletal survey [3]. On PET/CT scans, the presence of focal or diffuse areas of detectable increased tracer uptake on at least two consecutive slices was recorded in 9.5% (37/390) of MGUS patients. The most frequent pathology was lymphadenopathy 3.8% (15/390), followed by thyroid disorders 2.1% (8/390), and rheumatic diseases 1.8% (7/390). Primary malignancy was confirmed by histological verification in 4.8% (19/390) patients. This included 3.1% (12/390) patients with lymphoproliferative diseases and 1.8% (7/390) patients with solid tumors.

Lymphadenopathy was the most common pathology, detected in 3.8% of evaluable patients. All patients with detected lymphadenopathy underwent biopsy of lymph nodes. Overall, 3.1% (12/390) of patients were reclassi-

fied as having lymphoproliferative diseases. Patients were divided into low risk and aggressive lymphoma according to WHO classification [26]. Among the remaining 3 patients with lymph nodes abnormalities, 1 patient was diagnosed with Sjögren's syndrome, 1 patient with sarcoidosis, and 1 patient with reactive lymphadenopathy, without the detection of malignant cells after the biopsy. None of the patients had symptoms typical for lymphoproliferative diseases at the time of PET/CT imaging.

Thyroid disease was the second most common pathology in our study, observed in eight (2.1%) patients. In one patient, thyroid carcinoma was diagnosed; the remaining seven (1.8%) patients were diagnosed with focal thyroid abnormalities, nontoxic struma. All patients had thyroid hormones tested within the normal range at the time of PET/CT imaging.

Rheumatologic diseases were the third most common pathology, occurring in seven (1.8%) of all scanned patients. Specifically, there were four (1.1%) patients diagnosed with rheumatoid arthritis, two (0.5%) patients with polymyalgia rheumatic, and one patient with giant-cell temporal arteritis. Schwannoma of the femoral nerve was identified in one case. The description of overall imaging findings in every patient with MGUS is provided in Table 2.

## Discussion

MGUS is a known precursor of more serious diseases, such as MM, MW, and primary amyloidosis, but most patients with MGUS do not develop a plasma cell malignancy [7]. However, numerous reports suggest an association of MGUS with a wide variety of other malignant and nonmalignant diseases [27–29]. Because of the high prevalence of MGUS in the general population, it is difficult to distinguish true pathogenic relationships from coincidental associations. In fact, approximately 3% of patients with any given disease will be found to have MGUS based on coincidence [30]. Furthermore, MGUS is one of the most common pre-malignant disorders, with the rate of progression to MM or related malignancies at approximately 1% per year [7–10].

Most experts do not routinely recommend imaging in MGUS patients with serum IgG M-protein of 15 g/l or < or IgA M-protein of 10 g/l or < without bone pain. For all other patients with apparent conventional MGUS, imaging should be considered (skeletal survey for non-IgM M-protein; CT scan of chest, abdomen, and pelvis for IgM MGUS) [31].

However, since MGUS may be connected to an increased risk of developing hematologic as well as solid malignancies or other disorders, we believe that all newly diagnosed MGUS patients should be evaluated by PET/CT imaging. We are aware that the PET/CT imaging is associated with higher radiation exposure than many other conventional diagnostic radiology examinations. On the other hand, we know that MGUS is rare in young patients (pts; age <40 years at diagnosis), with a prevalence of <0.3%, representing

**Table 1. Patients' clinical and laboratory characteristics.**

Clinical characteristics	Number of patients (%)	
<b>Sex</b>		
females		206 (52.9%)
males		184 (47.1%)
<b>Age (at diagnosis)</b>		
younger than 50		60 (15.4%)
50–59		96 (24.6%)
60–69		116 (29.7%)
older than 69		118 (30.3%)
<b>M-protein type</b>		
IgG		271 (69.6%)
IgM		54 (13.8%)
IgA		48 (12.2%)
biclonal		13 (3.2%)
other		4 (1.1%)
<b>Light chain type</b>		
kappa		225 (57.7%)
lambda		150 (38.4%)
biclonal		15 (3.9%)
<b>Immunoparesis</b>		
Yes		98 (25.2%)
No		292 (74.8%)
<b>M-protein in serum (g/dl)</b>	≥1.5	48 (12.4%)
	<0.26	
<b>Kappa/lambda ratio</b>	or >1.65	169 (43.4%)
<b>BMPC infiltration – cytology (%)</b>	>5	49 (12.6%)
<b>BMPC infiltration – histology (%)</b>	>5	51 (13.0%)
<b>Albumin (g/dl)</b>	<3.5	18 (4.6%)
<b>Beta2 microglobulin (mg/l)</b>	>3	76 (19.5%)
<b>Hemoglobin (g/dl)</b>	<12	63 (16.1%)
<b>LDH (μkat/l)</b>	>3.75	145 (37.2%)
<b>Platelets (10E9/l)</b>	<150	30 (7.6%)
<b>Creatinine (μmol/l)</b>	>115	49 (12.6%)
<b>Calcium total level (mmol/l)</b>	>2.2	340 (87.1%)
<b>Normal PC – CD19+ (%)</b>	≤5	101 (26.0%)
<b>Abnormal PC – CD56+ (%)</b>	≥95	19 (4.8%)

Abbreviations: M-protein, monoclonal-protein; Ig, immunoglobulin; BM, bone marrow; PC, plasma cells; Immunoparesis: IgA <0.61 g/l, IgG <7.67 g/l, IgM <0.5 g/l;

approximately 2% of all patients with MGUS [2]. Therefore, we hypothesized that the presence of monoclonal immunoglobulin in young patients may be associated with a higher risk of malignant or nonmalignant diseases [32]. Despite the higher radiation exposure, we believe that PET/CT imaging should be recommended also for young newly diagnosed MGUS patients.

On PET/CT scans, the presence of focal or diffuse areas of detectable increased tracer uptake was recorded in 37 (9.5%) MGUS patients. The most common detected pathology was lymphadenopathy (3.8%) followed by thyroid diseases (2.1%), rheumatic diseases (1.8%), and other solid tumors (1.5%).

The association of MGUS and well-differentiated B-cell NHL is a well-known phenomenon [33–36]. Already in 1978, Lennert et al. reported that approximately 20% of all patients with lymphoplasmacytic lymphoma have serum monoclonal immunoglobulin [37]. The results of our study showed that nearly 4% (15/390) of all MGUS patients had lymphadenopathy, whereas 3.1% (12/390) patients were reclassified as having lymphoproliferative diseases after the biopsy. Five patients had low risk lymphoma and seven patients had aggressive lymphomas, Table 2.

Systemic autoimmune diseases, especially primary Sjögren's syndrome, are one of the best examples of non-hematological diseases, which often present with monoclonal gammopathy. In the 1980s, Moutsopoulos and later in 2012, Brito-Zerón [38–40] reported the presence of monoclonal immunoglobulins in Sjögren's syndrome patients and their association with extraglandular manifestations and lymphoproliferative disorders. Subsequent studies reported that up to 20% of patients with primary Sjögren's syndrome may be associated with MGUS [41]. In contrast, our study of 390 newly diagnosed MGUS patients revealed only one patient with newly recognized Sjögren's syndrome. As for the remaining two patients with lymph nodes abnormalities detected by PET/CT imaging, sarcoidosis was detected in one patient and reactive lymphadenopathy, without the detection of malignant cells after biopsy, was detected in the other patients. The association of sarcoidosis with MGUS or MM is not well described, but few cases of patients with both sarcoidosis and MM have been reported in the literature [42].

The second most common pathology in our study was thyroid disease, observed in 2.1% (8/390) of patients. Finally, 1.8% (7/390) of the patients presented with non-malignant thyroid disease, mainly nontoxic struma. Although thyroid disease is not frequently associated with MGUS, some studies presented an increased rate of this pathology in MGUS patients compared to the general population [43].

Rheumatic diseases were the third most common pathology, occurring in 1.8% (7/390) of all scanned MGUS patients. Specifically, there were 1.1% (4/390) of patients with rheumatoid arthritis, 0.5% (2/390) patients with polymyalgia rheumatic, and 1 patient with giant-cell temporal arteritis. It is known that specific rheumatic diseases have consistently been associated with MGUS. A Spanish study found rheumatic diseases to be the third associated pathology with a higher incidence of MGUS, after infections and heart diseases [44]. Significantly elevated risk of MGUS was found in patients with a history of all subcategories of autoimmune diseases and specific conditions, such as rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, pernicious anemia, immune thrombocytopenia, Guillain-Barré syndrome, celiac disease, chronic rheumatic heart disease, ankylosing spondylitis, polymyalgia rheumatica, giant cell arteritis, and aplastic anemia. A family history of autoimmune disease was associated with a significantly increased risk of MGUS, but not with MM. Both family history and personal history of autoimmune disease were independent predictors of risk of MGUS [45]. A population-based study had already shown the association of autoimmune conditions and the risk of

**Table 2. Patients' types of pathologies: histological subtypes.**

Types of pathologies	Description-Subtype	Number of patients
<b>Lymphadenopathy (n=15)</b>		
Lymphoproliferative diseases	CLL/small lymphocytic lymphoma	4
	Plasmablastic lymphoma	3
	Diffuse large B-cell lymphoma	2
	Hodgkin's lymphoma	1
	Burkitt's lymphoma	1
	MALT lymphoma	1
Diseases of the musculoskeletal system and connective tissue	Sjögren's syndrome	1
Inflammatory disease	Sarcoidosis	1
Other	Reactive lymphadenopathy	1
<b>Thyroid disease (n=8)</b>		
Non-cancerous	Nontoxic struma	7
Cancerous	Thyroid carcinoma	1
<b>Rheumatologic disease (n=7)</b>	Rheumatoid arthritis	4
	Polymyalgia rheumatic	2
	Giant-cell temporal arteritis	1
<b>Other malignancies (n=6)</b>	Colorectal cancer	4
	Prostate cancer	1
	Thymoma	1
<b>Other (n=1)</b>	Schwannoma of femoral nerve	1

specific lymphoid malignancies [46]. The specific mechanisms are not well understood but chronic antigen stimulation assumes an important role [47, 48].

While MGUS patients are known to be at an increased risk of developing MM, MW, and primary amyloidosis, the risk of developing non-hematologic malignancies is less clear. A recent report suggested that MGUS patients have a 1.56-fold increased risk of developing non-hematologic malignancies. In 2011, Mailankody et al. reported an increased risk for people with MGUS of developing non-melanoma skin, endocrine, breast, kidney and urinary tract, respiratory, male reproductive system, and GI cancers [11]. In our study, 1.8% (7/390) of the newly diagnosed MGUS patients presented with solid malignancies. The most common malignancy was colorectal cancer in 1.0% (4/390) of the patients followed by prostate and thyroid cancer, which were present in one patient each. Thymoma was diagnosed in one patient. Our findings particularly reflected results from the Czech National Cancer Registry. Czech men are most frequently affected by prostate cancer, closely followed by colorectal and lung cancer. The most frequent diagnoses in Czech women are breast cancer, followed by colorectal, lung, and uterine cancer. Contrary to previous reports [11], we did not find other solid malignancies, such as breast or lung cancer, in our group of MGUS patients.

Our study is the first report of the PET/CT imaging in MGUS patients. In 390 evaluable MGUS patients, we documented nearly 10% of patients with malignant and nonmalignant disorders, including aggressive lymphomas and solid tumors. We want to emphasize that all MGUS patients with newly detected illnesses at the time of PET/CT imaging were asymptomatic at the time of the scan. Because of PET/CT imaging, we were able to detect unexpected disorders in these patients – at the time when these patients showed no symptoms. Despite the fact that PET/CT imaging is an expensive diagnostic procedure and its availability is limited, we strongly recommend its usage in all newly diagnosed MGUS patients regardless of type and size of M- protein.

In conclusion, MGUS is a premalignant plasma cell disorder that may progress into multiple myeloma, Waldenström macroglobulinemia, or other lymphoproliferative disorders. Our findings clearly suggest this association. We detected nearly 10% of patients with serious illnesses – before the first symptoms – in newly diagnosed MGUS patients. Our results show that PET/CT imaging can be recommended not only for MGUS patients with suspected SMM or active MM but also for all newly diagnosed MGUS patients with aim of early detection of other disorders.

**Acknowledgments:** The authors would like to thank all colleagues who are involved in the care of MGUS patients, especially to doctors at the Masaryk Memorial Cancer Institute, from the Department of Nuclear Medicine for their excellent cooperation.

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