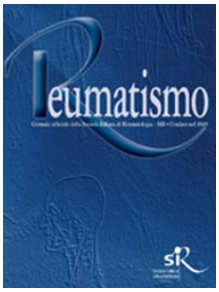

Reumatismo - The Italian Journal of Rheumatology

https://www.reumatismo.org/reuma

eISSN 2239-7132

Please cite this article as:

Scriffignano S, Perrotta FM, Ricci M, et al. **Visceral muscle dysmotility syndrome in systemic lupus erythematosus: which is the role of 18 fluorodeoxyglucose-positron emission tomography-computed tomography? A clinical case and literature review**. *Reumatismo* doi: 10.4081/reumatismo.2024.1647

Submitted: 13-09-2023
Accepted: 01-05-2024

Visceral muscle dysmotility syndrome in systemic lupus erythematosus: which is the role of 18 fluorodeoxyglucose-positron emission tomography-computed tomography? A clinical case and literature review

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Key words: systemic lupus erythematosus, visceral muscle dysmotility syndrome, generalized megaviscerous of lupus, 18 fluorodeoxyglucose-positron emission tomography-computed tomography.

Contributions: SS, EL, prepared the manuscript, FMP, revised the manuscript; MR, BC, contributed to the analysis of imaging data; all authors contributed to revising the manuscript.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: this study involves human participants and was approved by the Ethics Committee (Protocol n. 0001-017-2021, IRB-University of Molise).

Patient consent for publication: patient consent was obtained for the publication of her clinical history.

Funding: none.

Availability of data and materials: data are available from the corresponding author upon request.

Acknowledgments: the authors would like to thank their patient for giving them the opportunity to describe her clinical story.

Summary
Visceral muscle dysmotility syndrome (VMDS) is a rare syndrome, described in the systemic lupus erythematosus (SLE) clinical course. It is characterized by diffuse thickened intestinal wall and gastrointestinal-genitourinary-hepatobiliary hollow viscera dilatation and dysmotility. Due to the rarity and the heterogeneity of the clinical characteristics of this syndrome, it is not entirely clear which is the best diagnostic imaging technique for the diagnosis and/or follow-up, even if, in all the described cases, computed tomography (CT) was generally used to study visceral involvement. However, there are no cases describing the visceral metabolic activity by 18 fluorodeoxyglucose (18FDG)-positron emission tomography-CT (18FDG-PET-CT). Here, we reported the first clinical case of VMDS studied by 18FDG-PET-CT, characterizing the metabolic activity of this rare syndrome during SLE flare. We found a high intestinal metabolic burden, hyper-fixation in duodenum, and high hepatic metabolic activity. Moreover, we reviewed the literature on VMDS in SLE, focusing on imaging techniques in different anatomical sites (bowel, urinary tract, bile ducts), patients' symptoms, and treatment.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune systemic chronic disease characterized by clinical variability: the disease spectrum ranges from very mild clinical manifestations to life-threating ones (1). Among the latter, a rare manifestation characterized by gastrointestinal, genitourinary, and hepatobiliary hollow viscera dilatation and dysmotility has been described. It was named generalized megaviscerous of lupus (2) or, more recently, visceral muscle dysmotility syndrome (VMDS) (3).

Even though VMDS is a rare clinical manifestation, it is peculiar to SLE; in fact, it has never been described in other systemic autoimmune diseases. Based on organ involvement, a complete form of VMDS, in which gastrointestinal, genitourinary, and hepatobiliary hollow viscera are involved, and an incomplete form characterized by intestinal involvement and uretero-hydronephrosis were described (3). The main associated symptoms are abdominal pain, vomiting, diarrhea, and constipation, due to an ineffective intestinal propulsion, configuring a pseudo-intestinal-obstruction clinical scenario (3).

Even though the specific pathophysiologic mechanisms beyond VMDS in SLE remain unknown, the involvement of multiple hollow visceral organs should raise the suspicion of a generalized autoimmune smooth muscle involvement (2). However, a clear association with a specific autoantibody profile remains lacking. Beyond pathophysiology, it is not entirely clear which could be the best imaging technique for the diagnosis/follow-up, even if, in all the described cases, computed tomography (CT) was used to study visceral involvement (Table 1) (2-9).

As far as we know, no clinical cases of VMDS have been assessed by 18 fluorodeoxyglucose (18FDG)-positron emission tomography-CT (18FDG-PET-CT), and looking at its possible use in VMDS, we hypothesized at least two advantages (compared to CT): an early diagnosis (because a high metabolic activity could herald the visceral dilatation/thickening) and a way to assess the treatment response (testing metabolic activity). Moreover, it is interesting to understand which organs have a higher metabolic involvement to open a new possible scenario on this rare syndrome. For these reasons, we decided to perform 18FDG-PET-CT on our patient with a known diagnosis of SLE during a SLE flare characterized by gastrointestinal symptoms.

Besides, we reviewed the English literature on VMDS in SLE using the Medline PubMed database (from January 1950 until June 2023), focusing on imaging techniques that involved different anatomical sites (bowel, urinary tract, bile ducts), patient symptoms, and treatment. The terms used for the search were: “visceral muscle dysmotility syndrome, systemic lupus erythematosus”, “generalized megaviscera, systemic lupus erythematosus”, “intestinal pseudo-obstruction, uretero-hydronephrosis, bile ducts dilatations, systemic lupus erythematosus”.

Case Report

A 36-year-old woman, affected by SLE for 6 years, was admitted to the emergency room of our hospital (April 2023) due to abdominal pain, vomiting, and diarrhea alternating with constipation. These symptoms lasted for approximately 3 months, but the patient, due to their sporadic occurrence (3/4 times a month), did not request any medical consultation. The frequency of the symptoms increased in the last 3 weeks before the admission. At that time the patient was on prednisone 5 mg/day and hydroxychloroquine 5 mg/kg/day.

Medical history

Her past medical history started when she was 30 years old. At that time, she had arthralgia and thoracic pain that brought her to the emergency room: pericardial effusion was found. Antinuclear antibodies (ANA) and double-stranded (ds)DNA-antibodies were positive, extractable nuclear antigen antibodies negative, and there was a reduction of the complement concentrations and proteinuria (1 g/24). Unfortunately, a renal biopsy was not performed and no other anamnestic information is available on her renal involvement. During the assessment of her medical history, she also reported photosensitivity.

Therefore, a SLE diagnosis was posed, according to the American College of Rheumatology classification criteria (10); the SLE Disease Activity Index 2000 (SLEDAI-2K) was 10, indicating active disease (11). Treatment with glucocorticoids (metilprednisolone 500 mg i.v. for 3 days and then oral prednisone), hydroxychloroquine (5 mg/kg/die), and mycophenolate (until 2 g/die) was started. After 6 months, the patient achieved remission (SLEDAI-2K: 2) and complete renal response.
Her clinical history (2018-2020) was complicated by knee septic arthritis, that suggested to stop mycophenolate, and by avascular necrosis of the femoral head, treated with total hip replacement. After the resolution of these complications, the patient had good disease control on prednisone 5 mg/day and hydroxychloroquine 5 mg/kg/day, until January 2023, when her gastrointestinal symptoms started.

Current symptoms

At admission to the emergency room (April 2023), a physical examination revealed a distended and tender abdomen, tympanic sound on percussion, absent peristalsis on auscultation, and bi-basal pulmonary dullness. Abdominal contrast-enhanced CT was performed, and diffuse wall bowel thickening was found (Figure 1a.1 and a.2). The surgeons on duty ruled out intestinal obstruction and referred to our unit for a rheumatological consultation due to her clinical history. Assuming an SLE flare, we suggested performing a serological evaluation and assessing the abdominal metabolic activity by a total-body 18FDG-PET-CT. It confirmed the diffuse wall bowel thickening and showed inhomogeneous and diffuse tracer hyperfixation in the intestinal area, with a higher fixation in the duodenum (Figure 1b.1 and b.2). Moreover, diffuse and inhomogeneous tracer uptake was present in the hepatic area. There was a severe dilatation of the ureters bilaterally (max right ureter diameter: 1.71 cm) and to a lesser extent of the renal pelvis (Figure 1c.1-1c.2). Finally, generalized serositis was present with perihepatic, perisplenic, pericardial, peritoneal, and pleural effusions increased tracer uptake with nuanced pattern (Figure 1d).
Blood tests revealed: ANA 1:2560 (fine speckled profile), positive anti-ribonucleoprotein antibodies and anti-Sm antibodies (81 U.A./mL and 186.5 U.A./mL, respectively), positive anti-dsDNA, low complement level (C3= 40 mg/dL, C4= 6 mg/dL), low serum albumin level (2,5 g/dL), leucopenia [white blood cells (WBC): 1500/uL, neutrophils (N) 900/uL, lymphocytes (L) 250/uL], and hypochromic microcytic anemia [hemoglobin (Hb) 8.7 g/dL].
Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ glutamyl-transferase (γGT) were three times above the normal range. Creatinine, C-reactive protein, erythrocyte sedimentation rate, and urinalysis were normal.

Diagnostic workout and treatment

The clinical scenario suggested a SLE flare: the first diagnostic hypothesis was of lupus enteritis, but considering the contextual dilatation of the ureters, we favoured the diagnosis of an incomplete form of VMDS. Therapy with i.v. methylprednisolone was started: 500 mg/day for three days, followed by oral prednisone (starting dosage 0.5 mg/kg/day), and azathioprine 2 mg/kg/day; the patient was already on hydroxychloroquine, which was continued. Two days after the first methylprednisolone infusion, the patient's abdomen was less globular with initial recovery of peristalsis, resolution of abdominal pain and vomiting. After one month of therapy, the patient did not complain of any gastrointestinal symptoms. AST, ALT, and γGT values returned to normal, and the blood cell count improved both for leukopenia and anemia, with WBC: 3920 (N: 2940, L: 670), and Hb: 10.7 g/dL.
At the follow-up CT examination (40 days after treatment start, with a prednisone dose of 0.4 mg/kg/die), the intestinal wall thickening was markedly reduced in all segments (Figure 1e) and the pleural effusion was absent (Figure 1f) with a simultaneous normalization of the diameter of the ureters and renal pelvis. However, there was a diffuse colon distension by gas. At the follow-up visit in September 2023, the patient reported normal bowel habits, the physical examination was normal, and serological tests were

normal, except for positive anti-dsDNA and C3=60 mg/dL, C4=8 mg/dL. Belimumab 200 mg/weekly was added as steroid-sparing agent when prednisone dose was 0.2 mg/kg/die. At the last follow-up in December 2023, clinical remission was maintained, and the treatment with hydroxychloroquine, azathioprine, and belimumab was continued, with a steroid dose of 0.1 mg/kg/every two days.

Discussion and Conclusions

We describe a case of SLE flare characterized by incomplete VMDS, assessed by 18FDG-PET-CT and treated with glucocorticoids, azathioprine, and belimumab; at the last follow-up, there was a good clinical-imaging-serological improvement. We found a high intestinal and hepatic metabolic burden; in particular, the highest activity was recorded in the duodenum. This characteristic could remind of lupus enteritis, another clinical rare entity that can complicate the SLE course.

As mentioned above, one possible advantage of 18FDG-PET-CT rather than CT could be the earlier identification of bowel involvement, since we believe that metabolic activity precedes the structural bowel change of thickening and dilatation, and the possibility of assessing the treatment response in terms of metabolic activity. Unfortunately, we did not have the opportunity to test these two hypotheses because when 18FDG-PET-CT was performed, the bowel thickening and dilatation were already present, and we did not perform a control 18FDG-PET-CT to assess treatment response.

However, by using 18FDG-PET-CT, we objectify an intriguing characteristic: diffuse intestinal tracer uptake, with a higher fixation in the duodenum. This finding confirms a diffuse increase in intestinal metabolic activity, but it is still unclear why the duodenum was more involved than other gastrointestinal tracts. If this finding is confirmed in other cases, it could improve our understanding of the pathologic mechanism beyond VMDS.

Moreover, in our case, also the hepatic cells showed an increased metabolic activity, associated with increased serum liver enzyme concentrations. The role of hepatic involvement in VMDS is unclear because it was not previously described. Looking at ureters, generally involved in VMDS, it was interesting to note that they were dilatated, but without tracer uptake increase. In this case, the possibility of a “secondary” hydrouretero-nephrosis due to peritonitis should be considered, in contrast with the previous hypothesis of a generalized autoimmune smooth muscle involvement (2).

Therefore, all these findings may raise the question of which anatomical sites are predominantly inflamed in VMDS, and 18FDG-PET-CT could be useful to address this question. In our case, 18FDG-PET-CT showed a predominant intestinal involvement. This could support the definition of VMDS as lupus enteritis (12) complicated by hydroureteronephrosis and/or hepatobiliary hollow viscera dilatation. However, to support this hypothesis, future studies are needed to understand the pathogenetic mechanism beyond both VMDS and lupus enteritis. In fact, as reported in Table 1, only a few VMDS cases were described and, due to their phenotypic heterogeneity, it is difficult to identify clinical and serological features preceding visceral involvement and a standardized approach to the disease.

In conclusion, we characterize the metabolic activity in a case of VMDS by using 18FDG-PET-CT, showing a high intestinal and hepatic metabolic burden. If 18FDG-PET-CT is used in other similar cases, we will probably better understand some aspects of this rare syndrome.

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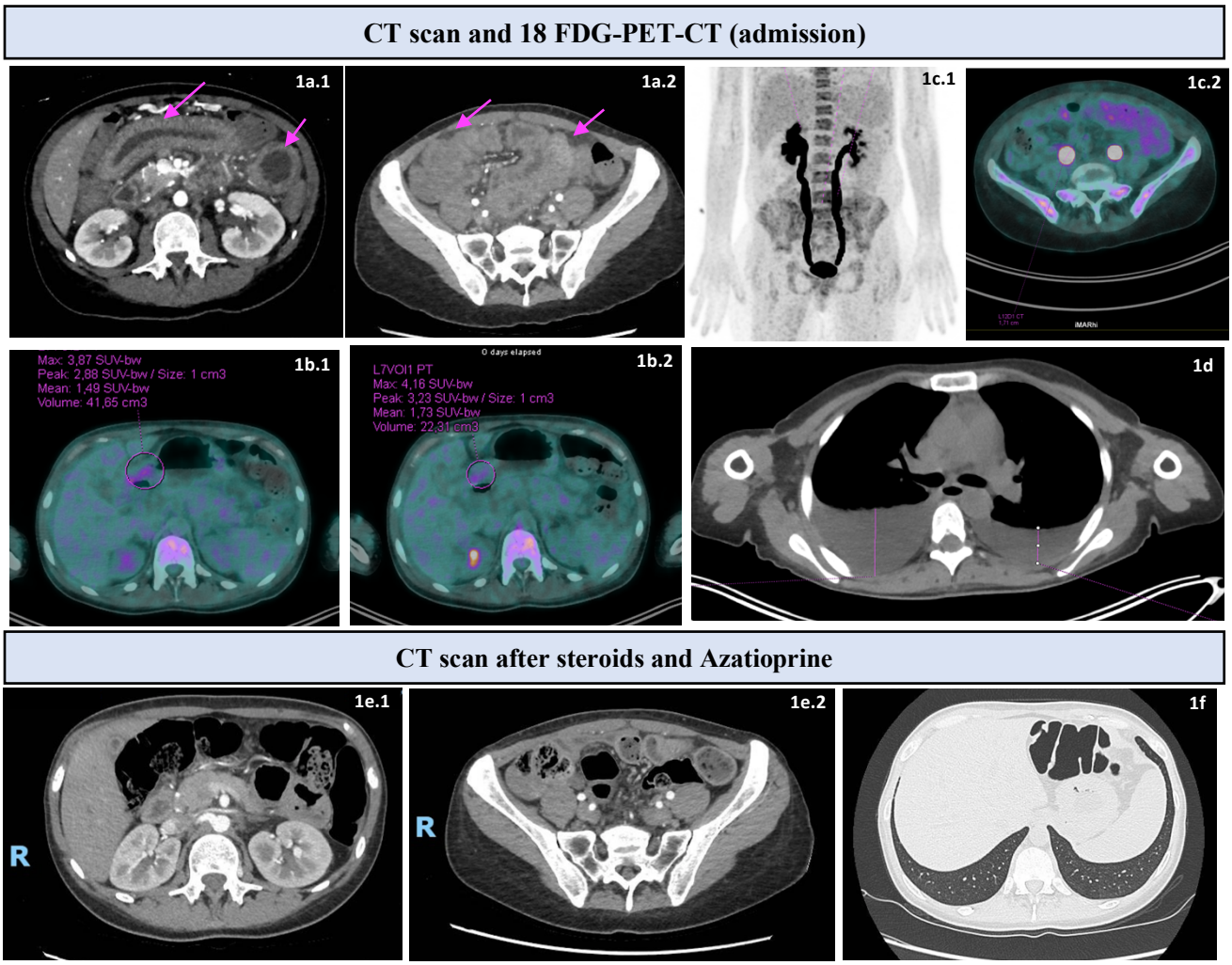

Figure 1. Contrast-enhanced abdominal computed tomography (CT) scan and 18 fluorodeoxyglucose (18FDG)-positron emission tomography-CT (18FDG-PET-CT) images before and after treatment. 1a.1, a.2) CT scan of the abdomen: diffuse thickening of the intestinal walls (small bowel and descending colon); 1b.1, b.2) PET/CT examination with standard and late [18F] FDG uptake (at 120 minutes). Tracer hyper fixation in the duodenal area: standard acquisition (1b.1) (SUVmax 3.87), late acquisition (1b.2) (SUVmax 4.16); 1c.1) portion of the MIP (Maximum Intensity Projection) image of the PET/CT exam with [18F] FDG: dilatation of the ureters bilaterally; 1c.2) CT of low-dose co-registration of the PET/CT examination. Dilated ureters: right ureter (maximum transverse diameter 1.71 cm); 1d) pleural effusion more pronounced on the right side; 1e.1, e.2) CT scan of the abdomen: reduced wall thickening at the level of the colon and small bowel; fecal and air distension of the transverse colon; 1f) chest CT examination: disappearance of the pleural effusion.

Table 1. Summary of the revised literature. For each study, the number of patients, age, sex, imaging techniques, anatomical site involvement, clinical symptoms and treatments are listed.

Patients	Imaging technique used		Anatomical sites involved			Symptoms	Treatment	Publication year (ref.)
	Diagnosis	Follow-up	Bowel	Urinary tract	Bile duct			
32-year-old-women	Abdomen CT scan Cystoscopy	Abdomen CT scan	x	x		Fatigue, vomiting, abdominal pain, diarrhea, dysuria.	High dose steroids, i.v. cyclophosphamide.	2004 (5)
57-year-old women	Gastroscopy Abdomen ultrasound Abdomen CT scan MRCP	Abdomen CT scan MRCP	x	x	x	Abdominal pain, intermittent diarrhea, weight loss, arthritis.	High dose steroids, i.v. cyclophosphamide, prokinetic, antibiotics, mycophenolate.	2005 (6)
46-year-old-women	Abdomen X-ray Abdomen CT scan Abdomen MRI Nephro-uretero-cystogram MRCP	n.a.	x	x	x	Abdominal discomfort and distension, constipation, arthralgia.	High dose steroids i.v. cyclophosphamide, i.v. immunoglobulin, mycophenolate, parenteral nutrition.	2009 (2)
24-year-old women	Abdomen CT scan Abdomen MRI MRCP	Abdomen CT scan	x	x	x	Recurrent vomiting, diarrhea, jaundice, constipation, abdominal pain.	High dose steroids, i.v. immunoglobulin, i.v. cyclophosphamide, total parenteral nutrition.	2012 (3)
27-year-old women	Abdomen X-ray Abdomen CT scan	Abdomen X-ray	x	x	x	Abdominal pain, recurrent vomiting, constipation.	High dose steroids, i.v. cyclophosphamide.	2012 (7)
32 patients. Mean age 29.7-years-old; female 87.5%.	Abdomen CT scan Abdomen ultrasound Abdomen X-ray	n.a.	x	x		Symptoms of intestinal obstruction	High dose steroids, i.v. cyclophosphamide, ciclosporin A, mycophenolate, i.v. immunoglobulin.	2015 (4)
21-year-old women	Abdomen contrast enhanced CT Colonoscopy	Abdomen CT scan	x	x	x	Abdominal distension, stenosis of sigmoid colon.	Surgery to treat stenosis.	2022 (8)
28-year-old women	Abdomen X-ray Abdomen contrast enhanced CT	n.a.	x	x	x	Abdominal pain, distension, vomiting, constipation.	High dose steroids.	2023 (9)

CT, computed tomography; MRI, magnetic resonance imaging; MRCP, Magnetic resonance cholangiopancreatography.