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Case Report

A Latent Autoimmune Diabetes in Adults Patient Manifesting Severe Musculoskeletal Complications

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Patients with diabetes have many different kinds of complications involving multiple organs, but those involving the musculoskeletal system are relatively uncommon. Diabetic muscle infarction (DMI) is a rare, painful, and potentially serious condition in patients with poorly controlled diabetes mellitus. A 35-year-old man diagnosed with type 2 diabetes eight years ago, visited with severe muscle pain in the right anteromedial thigh without any event of trauma. He had been treated with metformin, but his glycemic control was very poor with a glycated hemoglobin of 14.5%. Evaluation of his painful thigh lesion did not reveal any evidence of infection or vasculitis, but the magnetic resonance imaging and bone scan showed findings of DMI at vastus medialis muscle and an insufficiency fracture at the right medial tibial condyle. He was diagnosed with retinopathy, neuropathy and microalbuminuria but not macrovascular complications. We also diagnosed his diabetes as latent autoimmune diabetes in adults (LADA) based on his low C-peptide level, positive anti-glutamic acid decarboxylase (GAD) antibody and early onset diabetes. Instead of antibiotics, bed rest, analgesics and strict blood glucose control with multiple daily insulin injections led to symptom improvement. This is an unusual case of a young man with LADA experiencing severe musculoskeletal complication of DMI and insufficiency fracture. If a poorly controlled diabetic patient appears to have unaccounted soft tissue pain, musculoskeletal complications such as DMI associated with hyperglycemia should be considered.

Key Words: Diabetic muscle infarction, Insufficiency fracture, Latent autoimmune diabetes in adults

INTRODUCTION

Although there are many causes of muscle pain in diabetic patients, diabetic muscle infarction (DMI) is an unusual cause seen in patients with poorly controlled diabetes. DMI can be misdiagnosed as a variety of diseases that can produce muscle pain, such as myositis, localized abscess, hematoma, and deep vein thrombosis.[1,2] Here we report a case of DMI and insufficiency fracture in a 35-year-old man. We initially believed that his symptoms were due to soft tissue or muscle infection, but thorough examination led to the conclusion that the symptoms were due to DMI. The pathogenesis of DMI is not well established but it should be included in the differential diagnoses of diabetic patients with symptoms of muscle pain, especially in the thigh.

CASE

A 35-year-old man diagnosed with type 2 diabetes (T2D) eight years ago and treated with intermittent metformin administration visited our clinic. He had a history of a spontaneously healed ureteral stones ten years ago. He was 169.3 cm tall, weighed 51.6 kg, and his body mass index (BMI) was 18 kg/m^2. None of his family members had a known history of diabetes. He complained of a warm and painful lesion on his thigh for the last three weeks, but reported no recent history of trauma or injection. Initial physical examination of the painful lesion revealed tenderness and non-pitting edema of the anteromedial right thigh. His blood pressure and body temperature were 120/80 mmHg and 36.4℃, respectively. There was no leukocytosis (white blood cell count: 9,190/μL) and C-reactive protein was normal, but the erythrocyte sedimentation rate was elevated to 62 mm/hr. His glycemic control was very poor, with an HbA1c 14.5% and postprandial glucose of 446 mg/dL. Other biochemistry values were as follows: serum creatinine 0.4 mg/dL, blood urea nitrogen 24 mg/dL, potassium 4.6 mmol/L, sodium 132 mmol/L, calcium 9.1 mg/dL, phosphorus 3.6 mg/dL, alkaline phosphatase 86 U/L, albumin 4.1 g/dL, and creatinine kinase 436 mg/dL. He had proteinuria (trace) and glycosuria (4+) on urinalysis.

Serial blood culture showed no evidence of bacterial infection. As infectious causes were thought to be less likely, we conducted arterial and venous doppler ultrasonography of the extremity to exclude vascular problems such as deep vein thrombosis or peripheral artery disease. There was no evidence of vascular structural abnormality, but an ill-defined hyperechoic lesion and thick fluid collection in the right vastus medialis muscle was found. After four days, the amount of fluid increased, and thus fluid aspiration at the intermuscular fascial plane adjacent to the vastus lateralis was done (Fig. 1A, B). The fluid was clear, watery and serous. Gram stain and culture of the fluid were negative. Magnetic resonance image (MRI) of the right thigh reflected diffuse edema around the vastus medialis with low signal intensity on T1 (Fig. 2A, B) and high signal intensity on T2 images (Fig. 2C). The three-phase bone scan showed increased blood flow to the right thigh consistent with myonecrosis as shown on the thigh MRI (Fig. 3A, B). The bone scan also revealed increased blood flow at the right medial tibial condyle consistent with an insufficiency fracture, which was subsequently confirmed by X-ray and MRI (Fig. 4). Since these clinical findings and images were highly suggestive of DMI of the right vastus medialis with insufficient fracture of the right tibial condyle, a muscle biopsy was not performed.

Due to the early onset of disease (age 27), no obesity

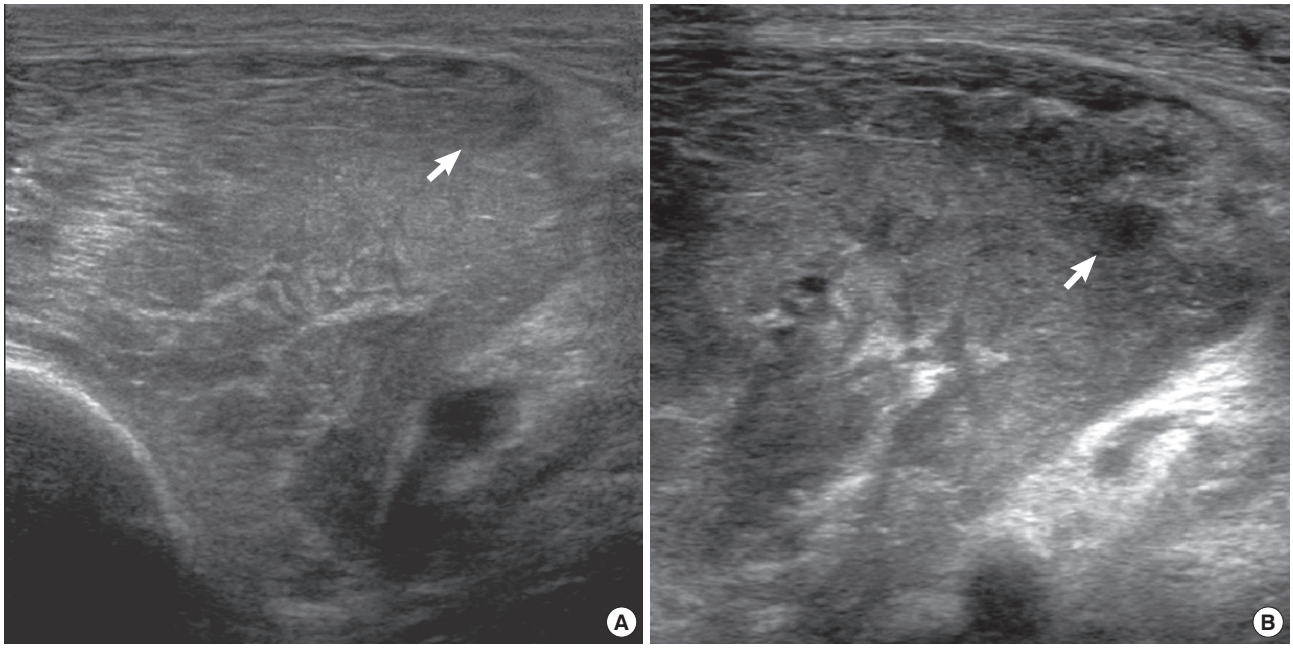

Fig. 1. Ultrasonography of the right thigh: (A) on admission, there was an ill-defined hyperechoic lesion and thick fluid collection (arrow) in the right vastus medialis. (B) After four days, there was an increase in the thick fluid collection (arrow) in the right vastus medialis.

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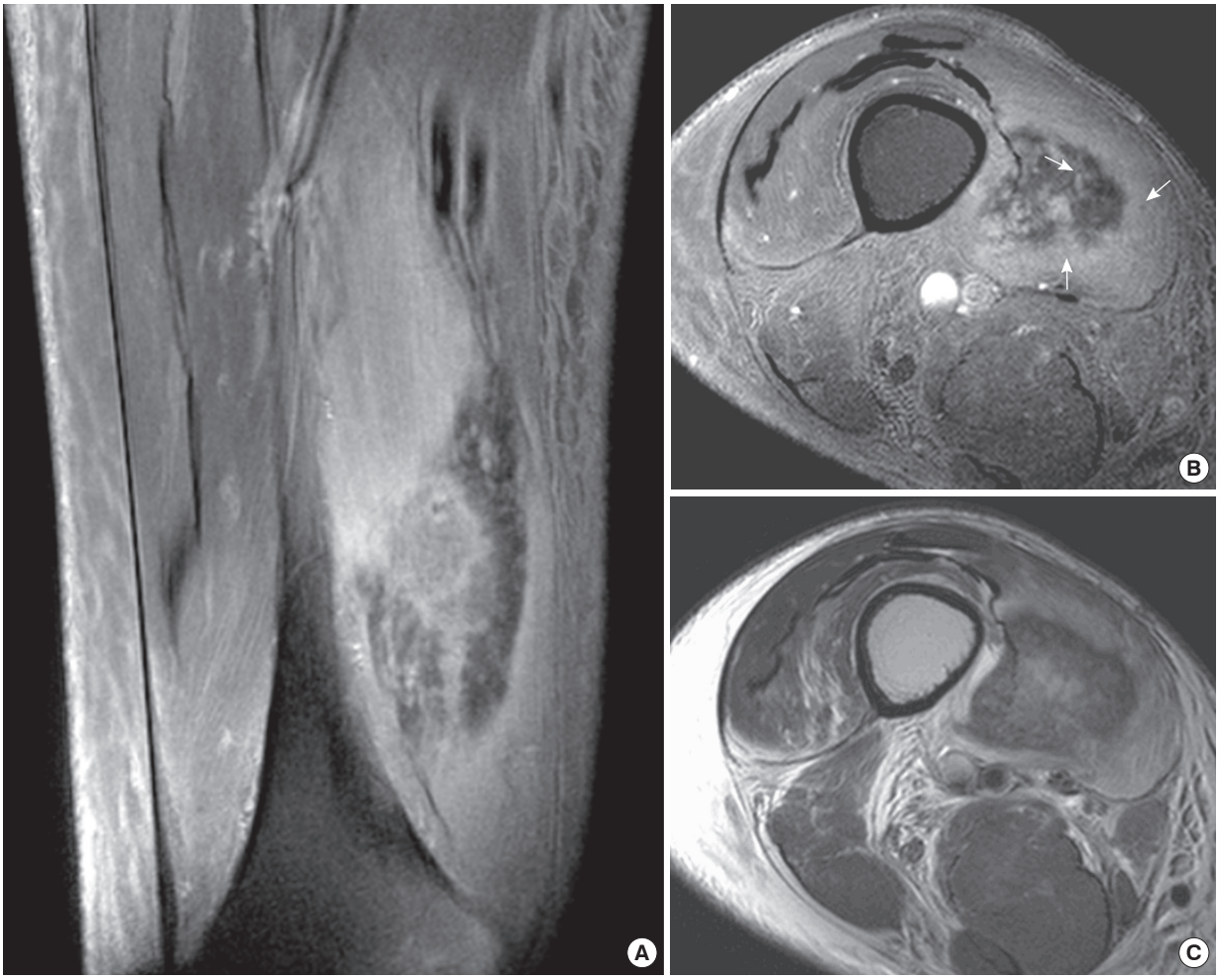

Fig. 2. Magnetic resonance image (MRI) of the right thigh: (A) Fat-suppressed, gadolinium-enhanced T1 coronal MRI revealed diffuse enlargement of the vastus medialis muscle with a low signal area at the distal part, suggestive of partly decreased perfusion, and edematous change of the proximal part. The low signal lesion at the distal part of the muscle had irregularly linear, serpentine enhancing portions crossing the lesion and surrounding peripheral enhancement. Diffuse subcutaneous edema involving the entire thigh was seen. (B) On the fat-suppressed, gadolinium-enhanced T1 axial image scanned at the distal part of vastus medialis muscle, irregular dark signal foci (arrows) and intervening enhancing portions were seen within the low signal lesion. Note the ill-defined peripheral enhancement. (C) T2 axial image showed high signal intensity at the low signal lesion of the same part in (B).

and no family history of T2D, we needed to clearly identify the exact type of his diabetes. Baseline C-peptide level was very low (0.1 ng/mL) and did not sufficiently rise at 6 min after glucagon stimulation test (0.3 ng/mL). Antinuclear antibodies, and anti-IA2 antibody results were not significant, but antibodies to glutamic acid decarboxylase (anti-GAD Ab) were positive (2.0 U/mL). Other immunologic factors were negative. Considering his age, low BMI, positive anti-GAD Ab, and severely decreased C-peptide level, we diagnosed his diabetes as a case of latent autoimmune diabetes in adults (LADA). After we examined microvascular and macrovascular diabetic complications, he was diagnosed with peripheral neuropathy and non-proliferative retinopathy of both eyes as well as microalbuminuria based on spot urine analysis (152 μg/mg Creatinine).

When we evaluated the cause of the insufficiency fracture, we found that his bone mineral density (BMD) was reduced, with T-scores of -3.9 (Z-score -3.3) at L1-L4 and -2.7 (Z-score -2.3) at the femur neck. Due to the young age of the patient, we also evaluated possible etiologies of secondary osteoporosis, including hyperparathyroidism, hyperthyroidism, hypogonadism, and glucocorticoid excess. 25-hydroxy-vitamin D (25-[OH]D) level was also lower than the normal limits (<4 ng/mL, normal range 11.1 to 42.9)

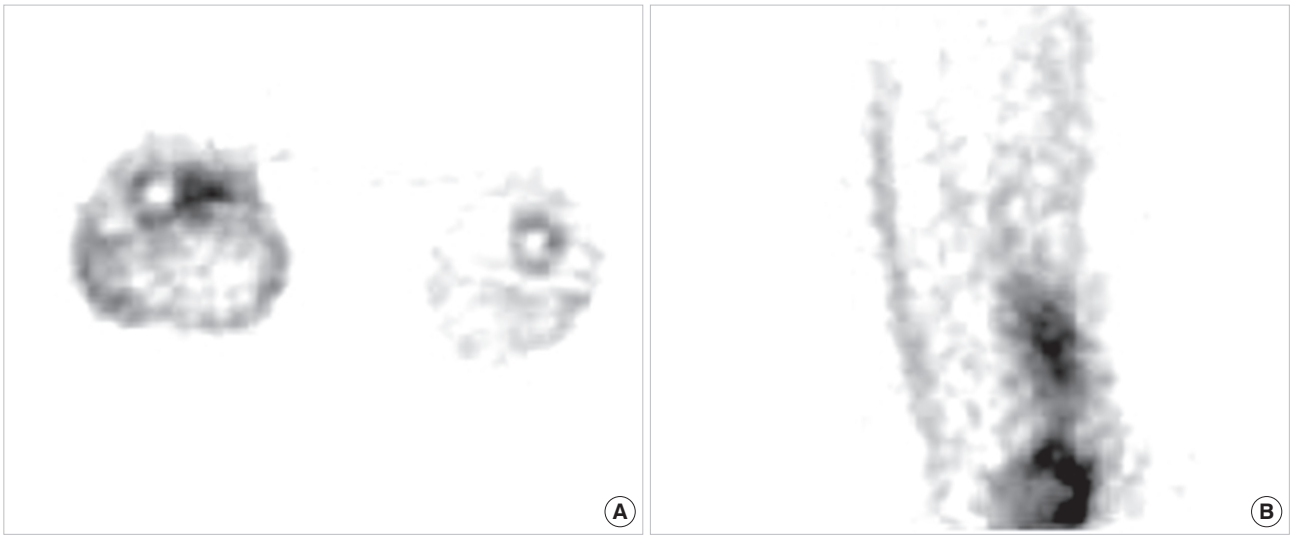

Fig. 3. (A) Cross-sectional view and (B) sagittal view of the three-phase bone scan: Increased perfusion, blood pool, and delayed uptake were seen at the right thigh, especially the lower medial portion of the right vastus medialis. This finding is consistent with myonecrosis as shown on the thigh magnetic resonance image.

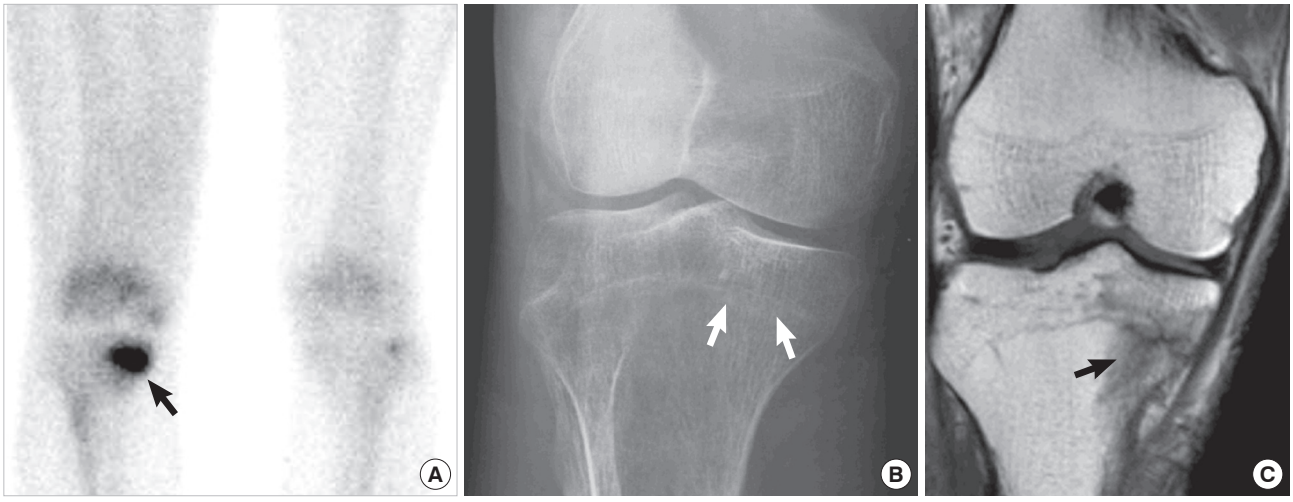

Fig. 4. Insufficient fracture of the right knee on multiple imaging studies: (A) Three-phase bone scan, (B) simple X-ray, and (C) Coronal T1-weighted magnetic resonance image (MRI). MRI showed serpentine low-signaled line with surrounding ill-defined low signal area at the right medial tibial condyle, which is consistent with insufficient fracture with marrow edema.

and osteocalcin level was slightly decreased (2.4 ng/mL, normal range 2.7 to 11.5). Thyroid function test was normal (free-T4 0.90 ng/dL, normal range 0.77 to 1.94 ng/dL; Thyroid stimulating hormone 2.24 μU/mL, normal range 0.30 to 4.00 μU/mL; T3 120 ng/dL, normal range 80 to 200 ng/dL), and there was no significant finding of thyroid autoantibodies. Parathyroid hormone (PTH) level was 19.6 pg/mL (normal range 13 to 54 pg/mL). C-telopeptide level was within normal limits (0.74 ng/mL, normal range 0.07 to 0.78 ng/mL). Testosterone and follicle stimulating hormone (FSH) levels were also within normal limits (Testosterone 2.19 ng/mL, normal range, 1.8 to 8.96 ng/mL; FSH 4.0 ng/mL, normal range, 2.8 to 9.6 ng/mL), with a slightly low luteinizing hormone level (1.3 ng/mL, normal range, 1.8 to 5.2 ng/mL).

Antibiotics were initially prescribed, but discontinued when bacterial infection was ruled out and DMI was thought to be the most likely clinical diagnosis. Instead, the patient was treated with analgesics such as acetaminophen, application of a long leg splint and bed rest, and multiple

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daily injections of insulin for strict glucose control. For his osteoporotic fracture, he was administered oral vitamin D and calcium agents. After about two weeks of supportive management, the tenderness and swelling of the right anteromedial thigh gradually reduced and the patient was able to walk without help, and so the splint was removed. 3 months later, when the hyperglycemia was controlled, we have done the oral glucose tolerance test and calculated the insulinogenic index (IGI, delta insulin 30 min - 0 min/ delta glucose 30 min - 0 min). Calculated IGI was 0 (reference range >0.5), which reflects diminished beta-cell function on glucose stimulation. On follow-up ultrasonography after 6 months, the myonecrosis of the right vastus medialis muscle was dramatically resolved and his HbA1c had improved to 5.7%. In addition, his 25-(OH)D level had risen to 58.7 ng/mL after 6 months of treatment. Five months after treatment, the patient complained of frequent injections, so we changed his insulin regimen to a premixed combination insulin injection twice a day. He is currently under follow-up at the outpatient clinic without any evidence of recurrence.

DISCUSSION

DMI is a rare but possible complication in patients with poorly controlled diabetes and progressed diabetic vascular complications.[3] It can be misdiagnosed as myositis, cellulitis or abscess; therefore, early detection is important in order to avoid unnecessary examinations and incorrect treatment.[1,2] DMI was first described in 1965 by Angervall and Stener[4] as "tumoriform focal muscular degeneration". Its pathophysiology is unclear, but several hypotheses have been suggested. First, the cause of DMI appears to be related to diabetic microvascular diseases since a considerable proportion of patients with DMI, like our case, have multiple end-organ microvascular diabetic complications.[3] Pathologic review reveals that conversion of the normal rich collateral circulation of muscle to an end-vessel circulatory pattern renders it particularly vulnerable to injury.[5] Secondly, vasculitis could be a factor in some instances of this syndrome; patients with diabetes are known to be susceptible to inflammatory vasculopathy.[6] It is well known that an autoimmune reaction is involved in the development of type 1 diabetes (T1D), and other nondiabetic autoimmune manifestations including vasculitis may be present in T1D patients.[7,8] Thirdly, Silberstein et al.[9] suggest that hypoxia-reperfusion injury may have an important role in the pathogenesis of DMI; an alteration in the coagulation-fibrinolysis system may cause microembolism which leads to the compartment syndrome, which produces ischemic muscle change. During the inflammatory response, hyperemia and reperfusion, reactive oxygen species are generated, which worsens the muscle damage. Anti-phospholipid antibodies perform roles as contributing factors in the progression of diabetes complications, acting as a link between the immunological and hemostatic systems in the pathogenesis of diabetic microangiopathy.[10]

The clinical presentation of DMI is uniform, with abrupt onset of painful swelling of the affected muscle, with or without a palpable mass.[3] DMI is diagnosed by a combination of clinical features and radiologic findings. MRI with gadolinium enhancement is thought to be most valuable in the diagnosis of DMI, and is characterized by an increased signal from the affected muscle area on T2-weighted images and isointense or hypointense signals on T1-weighted images after enhancement. There have also been a few DMI cases using bone scan at the initial diagnosis, with findings of increased blood flow and isotope accumulation at the involved muscle but not in the skeleton in common.[3,11,12] If the diagnosis is unclear, muscle biopsy may be needed to confirm DMI. However, in the case we describe, DMI was confirmed by clinical and radiologic findings, so a muscle biopsy was not performed. Treatment includes strict glucose control, bed rest, analgesics, and nonsteroidal anti-inflammatory drugs. Some recommend antiplatelet agents or glucocorticoids. The short-term prognosis of DMI is good, but the recurrence rate is relatively high, up to 47%, meaning long-term prognosis is poor.[1,3]

In our patient, there was evidence consistent with LADA with positive anti-GAD Ab. The patient was diagnosed as T2D when he was 27 years old. The patient was not obese, and had no known family history of diabetes. After diagnosis, he had been treated with metformin for eight years, and his diabetes was well controlled. However, hyperglycemic symptoms, such as polyuria and polydipsia, and the symptoms of DMI appeared in the three weeks before he visited the clinic. The clinical history and the laboratory findings correspond to the diagnostic criteria of LADA.[13] When a patient of T2D, without typical obesity or family

history, abruptly shows unusual clinical manifestations like DMI, other type of diabetes such as LADA should be considered.

Meanwhile, our patient revealed an insufficient fracture with osteoporosis as another musculoskeletal complication. Patients with diabetes, regardless of type, have an increased risk of fracture compared to people without diabetes.[14] The pathophysiologies of hyperglycemia on increased fracture risk are known to be quite different between types. In T1D patients, insufficient skeletal mineralization may contribute to the low BMD.[15] On the other hand, the adverse effects of hyperglycemic state on the skeletal systems of T2D patients are considerably counteracted by the positive effects of obesity on BMD. However, patients with T2D have an increased fracture risk despite a higher BMD, mainly caused by the increased risk of falls.[16] In a British study, older T2D women with a history of falling tended to show reduced vibration perception.[17] Setting aside his uncontrolled diabetes, our patient's 25-(OH)D level was significantly low. Vitamin D deficiency is common among many situations such as decreased sun exposure, insufficient dietary intake or malabsorption.[18] The patient reported spending most day time hours inside to prepare for a bar exam for almost for one year, resulting in scant sun exposure and consequently insufficient vitamin D synthesis. However, the low vitamin D level may be related to the diabetes itself. In some studies, T2D and other metabolic features have been connected to low 25-(OH)D levels. In a meta-analysis of 21 observational, cross-sectional studies, circulating 25-(OH)D levels showed an inverse association with T2D or metabolic syndrome.[19] Also 1,25-dihydroxyvitamin D is known to inhibit the production of various cytokines such as interferon-gamma, interleukin-2 (IL-2) and IL-12, and therefore potentially interrupting the initiation and progression of T1D or LADA mediated by T helper 1 cell.[20]

Based on our exhaustive literature review, this is the first report of DMI in a LADA patient. In a T2D patient showing severe and acute musculoskeletal symptoms, musculoskeletal complications related with hyperglycemia such as DMI should be considered, as well as the possibility of autoimmune diabetes including LADA.

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