the platelet count is less than 10,000 to 20,000/μL and severe thrombocytopenia usually occurs in association with disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, catastrophic APS, and heparin-induced thrombocytopenia.[6] In our patient, severe thrombocytopenia was primarily due to APS, and she did not fulfill the criteria for catastrophic APS.

Despite thrombocytopenia, there is always a risk for thrombosis, and there are reports of new thromboembolic events in APS patients with platelet counts ranging from 10,000 to 60,000/μL.[7] Our patient had features of thrombosis in the form of digital ischemia in toes and fingers, despite severe thrombocytopenia and active bleeding. As arterial Doppler findings were normal, she most likely had microthrombosis in the digits.

Hypertension is one of the manifestations of APS nephropathy. Hughes et al[8] described a group of patients with APS and hypertension, which ranged from mild elevation to malignant hypertension. Hypertension in our patient indicated that patient had renal involvement and it was controlled with antihypertensives.

Bleeding due to severe thrombocytopenia along with features of thrombosis is like a "Sword of Damocles" to the treating team. The presence of thrombocytopenia represents one of the few indications for immunosuppression in the management of APS. In severe thrombocytopenia, the first-line treatment is high-dose corticosteroid and/or IVIG and RTX; splenectomy can be also considered in severe cases. Sciascia et al[9] recently reported that sustained clinical remission of severe thrombocytopenia without immunosuppressive maintenance therapy was obtained by RTX alone in patients with APS and severe thrombocytopenia who were intolerant or refractory to conventional therapy. Gamoudi et al[10] reported 2 cases of APS-associated thrombocytopenia treated successfully with RTX, after patients did not respond to treatment with IVIG/steroids. In APS, not taking care of the clot may be life-threatening, while anticoagulation may cause hemorrhagic complications. Before introducing anticoagulants, platelet levels should be greater than 50,000/μL.[11] In our patient, we used a quadruple therapy of high-dose steroids, IVIG, RTX, and LMWH, and successfully controlled a life-threatening disease.

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Granulomatosis With Polyangiitis Cardiomyopathy Versus Myocardial Infarction

Value of Magnetic Resonance Imaging and Positron Emission Tomography for Differentiation

To the Editor:

CASE

A 56-year-old man was admitted for nausea and abdominal pain. At the time, laboratory studies revealed high lipase levels, and the patient was treated for acute pancreatitis with intravenous fluid and symptoms resolved. Later that month, he was readmitted for another episode of acute pancreatitis. Abdominal computed tomography showed bilateral lung base nodular infiltration, and abdominal magnetic resonance imaging (MRI) showed ischemia and necrosis of the pancreas. Lung biopsy revealed granulomatosis while urinalysis reported hematuria. Kidney biopsy showed crescentic glomerulonephritis. Titers for c-ANCA and PR3-ANCA were high positives (1.64 and 2.3). Rheumatoid factor was high (184). Negative laboratories for ANA, dsDNA, CCP, C3, C4, SSA, and SSB ruled out other autoimmune diseases. Anticardiolipin and lupus anticoagulant were not done as coronary thrombosis, and embolism were ruled out with results from imaging studies (there was a large area of myocardium involved with a multivessel distribution) and cardiac catheterization (normal). Furthermore, cardiac MRI did not show any thrombi in the heart or great arteries. During this admission, the patient reported chest pain and was diagnosed with pericarditis after troponin, cardiac catheterization, and echocardiogram were normal. The diagnosis of granulomatosis with polyangiitis (GPA) was then made, and the patient was started on prednisone at 1 mg/kg and rituximab at 325 mg/m^2 weekly.

Two months later, he was hospitalized for pancreatitis for a third time. At this visit, persistent diplopia, severe headache, right arm numbness, gait instability, and difficulty with speech was observed. A brain MRI showed an acute cerebellar and right parietal lobe infarct. Head and neck MRA showed mild but diffuse small vessel ischemic disease and small vessel vasculopathy. At that time, 2 months from the onset of symptoms, lung and kidney biopsy, positive c-ANCA, and PR3-ANCA results along with negative cardiac findings pointed to GPA as the cause of the cerebral infarction. Rituximab

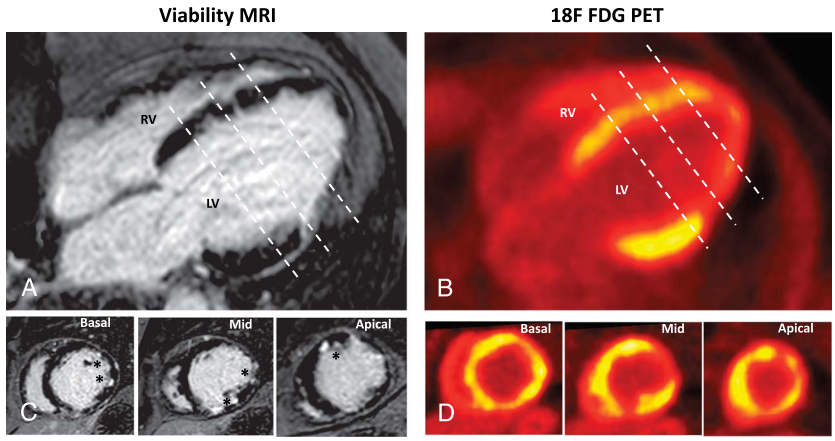

FIGURE. Cardiac magnetic resonance imaging in long and short axis planes (A and C on left) versus ^{18}F-FDG PET in the same orientation (B and D on right) showing subendocardial and transmural late gadolinium enhancement in the inferior, anterior, and lateral walls that very closely matches with regions of reduced to absent FDG uptake on ^{18}F-FDG PET consistent with myocardial fibrosis and loss of myocardial viability. Note the patchy subendocardial late gadolinium enhancement pattern on short axis magnetic resonance imaging slices (asterisk, panel C), which is very atypical and usually not consistent myocardial infarction due to obstructive epicardial coronary artery disease.

was discontinued, and cyclophosphamide was added to the patient 1 mg/kg daily dose of prednisone.

The patient responded well initially with improvement of symptoms and normalization of inflammatory markers. However, 3 months later, he developed heart failure symptoms including dyspnea on exertion, orthopnea, and pulmonary edema. An echocardiogram showed acute reduction in left ventricular ejection fraction from 50% to less than 35% over the course of 3 months along with regional wall motion abnormalities in a multivessel distribution.[1] Because the patient had a normal coronary angiogram 2 months prior, ischemic cardiomyopathy (ICM) was unlikely. Vasculitis was suspected as the most likely cause of these new symptoms. The patient was subsequently admitted to the hospital and underwent a cardiac MRI, which showed patchy subendocardial to near-transmural late gadolinium enhancement (LGE) consistent with myocardial fibrosis in a very atypical vascular distribution consistent with the working diagnosis of GPA. Takotsubo cardiomyopathy and microvascular angina were excluded due to the results of the cardiac MRI—specifically the LGE pattern and large infarcts. Without a left ventricle biopsy, the diagnosis of hemorrhagic myocarditis due to cyclophosphamide cardiotoxicity cannot be confirmed. However, our patient did not have the typical acutely fatal clinical course or timeline of symptoms usually associated with starting the medication.[2] In addition, our patient did not have the left ventricle wall thickening usually associated with cyclophosphamide cardiotoxicity according to our imaging studies.

Although MRI was able to provide an accurate assessment of myocardial fibrosis via LGE, complementary evaluation of myocardial inflammation was needed to justify further escalation of GPA therapy. Fusion metabolic imaging with ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) was therefore performed to assess for inflammation via labeled glucose uptake of activated macrophages within the gadolinium hyperenhanced areas on MRI. Fusion metabolic imaging with ^{18}F-FDG PET showed reduced ^{18}F-FDG uptake in the areas of LGE, consistent with lack of active inflammation and loss of myocardial viability apparently secondary to GPA. These findings indicated that an escalation of immunomodulating therapy would not be beneficial for the patient.

The patient was started on cardioprotective, goal-directed medical therapy and discharged with close outpatient follow-up. Since discharge, patient has done well from a heart failure perspective although he still occasionally exhibits NYHA class II symptoms. If the patient's ejection fraction remains low on follow-up cardiac MRI, he will be considered for a single-chamber implantable cardioverter defibrillator for primary prevention of sudden cardiac death.

Cardiac MRI in long and short axis planes (Fig. A, C; left) versus ^{18}F-FDG PET in the same orientation (Fig. B, D; right) showing subendocardial and transmural LGE in the inferior, anterior, and lateral walls that very closely matches with regions of reduced to absent FDG uptake on ^{18}F-FDG PET consistent with myocardial fibrosis and loss of myocardial viability. Note the patchy subendocardial LGE pattern on short axis MRI slices (asterisk, Fig. C), which is very atypical and usually not consistent myocardial infarction due to obstructive epicardial coronary artery disease. Images reprinted with permission from Asawaeer et al.[1]

DISCUSSION

Granulomatosis with polyangiitis commonly presents with upper and lower airway pathology as well as kidney involvement. Systemic disease can involve multiple organ systems including the nervous system, gastrointestinal tract, and the heart. Up until the 1970s, GPA was almost always fatal (80% mortality rate) and still has a high mortality rate if not treated.[3] Today, we have many immune-modulating therapies available to treat this condition including prednisone, cyclophosphamide, and biologic medications such as rituximab. In a rare situation GPA can cause myocardial involvement due to inflammation of the myocardium, which may manifest as cardiomyopathy and heart failure. In this setting, it is sometimes difficult to differentiate cardiac GPA from ICM. However, it is important that a clear diagnosis is made to guide treatment, maximize benefit, and avoid unnecessary toxicities and procedures.

A central problem in treating left ventricular dysfunction is differentiating between ICM and non-ICM (NICM). Traditionally, NICM has been diagnosed using chest roentgenography, standard 12-lead electrocardiography, transthoracic and/or transophageal echocardiography, coronary angiography, left ventriculography, and endomyocardial biopsy.[4] In the future, PET should be considered as a tool to evaluate the viability of cardiac tissue to determine the appropriateness of pharmacologic treatment of vasculitis or invasive cardiac intervention. Positron emission tomography imaging has not traditionally been included in the standard of care for these patients; however, it is capable of identifying cardiac tissue viability faster than standard imaging modalities. There is currently debate surrounding the benefit of using both MRI and PET to evaluate cardiac inflammatory diseases. New studies recommend that cardiac magnetic resonance should be used first while PET imaging should be used subsequently if needed to evaluate for active inflammation.[5] The combination of PET and computed tomography or MRI may detect inflammatory changes preceding structural damage, giving both metabolic and anatomic information. This combination can help differentiate a primary from secondary

cardiovascular pathology.[6] There are many genetic disorders where NICM diagnosis could be helpful in management and early access to medications and devices. Several autoimmune diseases including rheumatoid arthritis, scleroderma, sarcoidosis, ankylosing spondylitis, and systemic lupus erythematous have an increased risk of cardiovascular disease where the use of PET scan in addition to cardiac magnetic resonance could be useful in evaluation.[7] Cardiac sarcoidosis diagnosis in particular has traditionally been associated with challenges due to inconclusive results of endomyocardial biopsy.[8]

CONCLUSIONS

Granulomatosis with polyangiitis may present with symptoms, suggesting both cardiac and cerebral ischemia, which should be investigated for inflammatory process to determine the course of both acute and long-term treatment. We support the use of PET in addition to cardiac MRI as part of the standard of care for the workup of a patient presenting with cardiac ischemia symptoms in whom a history of vasculitis is suspected. In addition, PET can be a helpful tool in not only diagnosing GPA and the cause of pathologies, but also of monitoring response to pharmaceutical treatment. PET scans can show changes on a cellular level sooner than MRI and other methods, which can influence important changes to a patient's treatment.

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Digital Ischemia Induced by Fesoterodine

To the Editor:

Fesoterodine is an antimuscarinic agent used as a symptomatic treatment for polyuiria, urgency, or urinary incontinence consecutive to overactive bladder. Fesoterodine is converted to its metabolite 5-hydroxymethyltolterodine, which blocks peripheral M3 muscarinic receptors, especially on smooth muscle cells.[1,2] Reported adverse events include mouth dryness, dizziness, dyspepsia, and tachycardia. To the best of our knowledge, no vascular adverse event has been reported.[3] We report here the first case of digital ischemia induced by fesoterodine.

CASE REPORT

A 48-year-old nonsmoker woman with a previous history of yellow fever and thoracic and lower limb shingles presented to the outpatient clinic for digital ischemia. She had been followed up in our department for 7 months for a mixed connective tissue disorder according to Alarcon-Segovia, Kahn, Kasukawa, and Sharp criteria[4] with bilateral Raynaud phenomenon (RP) of the fingers and toes, associated with puffy fingers, peripheral inflammatory arthralgia, and mild interstitial lung disease, along with speckled antinuclear antibody (>5210 U/mL), anti-RNP, and anti-SSA antibodies (>241 and 233 U/mL, respectively). The capillaroscopy reported low-number homogeneous loops (8–10/mm), a pale aspect, some dilated loops, few periungual hemorrhage, and dystrophy, with no megacapillaries and no avascular areas. Her treatment included only hydroxychloroquine 200 mg twice a day and amlodipine 5 mg/d. Because of a detrusor overactivity confirmed on the urodynamic examination, she had been prescribed fesoterodine (4 mg/d). Two weeks after the first intake of fesoterodine, she noticed a worsening of her RP and presented to our outpatient clinic 2 months after.

At clinical examination, she presented with a painful digital ischemia predominant at the distal extremity of the first 3 fingers of the right hand. Allen maneuver and arterial Doppler ultrasound of the upper limb were normal. Fesoterodine was stopped, and a 4-day perfusion of iloprost (Ilomedine) was administered. The following days, we noticed a dramatic improvement of ischemia and resolution of pain. The patient did not experience another RP relapse over the next 3 months.

DISCUSSION

To the best of our knowledge, the present case is the first report of digital ischemia (DI) induced by fesoterodine in a patient with RP.

Raynaud phenomenon results from a disruption of the blood flow due to a constriction of arterial and arteriovenous anastomoses inflow.[5] This vasoconstriction is due to an increased sympathetic nervous response to low temperature and humidity. In connective tissue diseases, such as systemic sclerosis and mixed connective tissue disorder, underlying endothelial dysfunction and structural modifications also alter the integrity of the vessels. Indeed, a decrease of vasodilators, such as nitric oxide and prostacyclin, and an increase of thrombotic and proinflammatory cytokines and α2-mediated molecules, including an increased release of endothelin 1, favor vasoconstriction and disruption of the blood flow.[2] Herein, DI was caused by RP worsening, which could have been potentiated by the administration of fesoterodine. Indeed, fesoterodine is an anticholinergic drug that antagonizes muscarinic receptors, especially M3 receptors located on the bladder as well as on the vascular smooth muscle cells.[6] Consequently, it has the ability to inhibit the contraction of vascular smooth muscle cells by reducing the endothelium-dependent release of nitric oxide. It was therefore responsible for a limited vasodilation and a probable increased risk of DI in RP patients. Thus, the adverse drug reactions report made to pharmacovigilance was consistent with the probable imputability of fesoterodine.

To conclude, this is the first report of DI induced by fesoterodine. Practitioners using this treatment should be aware of this