

Multi-system Fibrosis and Long-term Use of Ergotamine

Dear Editor,

Multi-system fibrosis has been described in patients who chronically use ergotamine derivatives. It is a rare but important adverse effect of this class of drugs. Although the use of ergotamine derivatives has declined for the treatment of migraine and weight loss, they are increasingly used for other conditions such as Parkinson disease and sleep disorders. Clinicians may not be aware of their potential fibrosis related adverse effects in these settings. Hence, this case presentation aims at increasing clinicians' awareness of this potential adverse effect.

Case Report

A 43-year-old woman presented to a tertiary care facility with increasing shortness of breath and bilateral leg edema of 3 months duration. She had been healthy prior to these symptoms and her past medical history was only significant for intractable migraine that had been treated with topiramate, escitalopram and methadone. Her primary care physician has also prescribed ergotamine-caffeine suppositories as needed for breakthrough headaches. On average, she had used these suppositories 3 times per week for the last 12 years. Clinically, the patient appears to have congestive heart failure.

Echocardiography was performed and demonstrated that the leaflets of all valves were thickened with moderate regurgitation of the aortic valve and severe regurgitation of the mitral valve. The tricuspid valve leaflets were fixed in an opened position and there was profound tricuspid regurgitation. No intra-cardiac shunt was identified by color flow imaging. Doppler ultrasound of the lower extremities did not show deep venous thrombosis. Computed Tomography (CT) scan of the abdomen and pelvis revealed retroperitoneal fibrosis (mild diffuse thickening of the infrarenal abdominal aorta and iliac arteries, soft tissue thickening encasing the proximal inferior mesenteric artery and a diminutive inferior vena cava below the renal veins). The left common iliac vein was flattened and difficult to visualise. Images of echocardiography and CT scan of the abdomen and pelvis are depicted in figure 1. Twenty-four hour measurement of 5-Hydroxyindoleacetic acid (5-HIAA) was normal.

The clinical picture was consistent with multi-valvular

heart disease and retroperitoneal fibrosis due to the chronic use of ergotamine derivatives. The patient underwent mitral and tricuspid valve replacement. The aortic valve disease was considered moderate and managed medically. Pathology of valve tissue showed fibrocellular leaflet and cordal thickening. She opted for treatment with tamoxifen for the existing retroperitoneal fibrosis.

Ergot derived agents stimulate serotonergic receptors (5-HT_{2B}) causing proliferation of the myofibroblasts within an avascular myxoid matrix. These non-inflammatory degenerative changes affect several areas in the body such as the pleura, peritoneum, pericardium and heart valves. In the heart, pathology of affected valves demonstrates fibrotic proliferation that does not disrupt the structure of heart valves but leads to subsequent thickening of the leaflets and the chords.^{1,2} The resultant changes are similar to those observed in carcinoid syndrome; however, left sided involvement of the heart in carcinoid is rare and is usually associated with intra-cardiac shunts.³

The drugs known to be associated with these adverse effects are anti-migraine ergot alkaloid agents such as ergotamine and methysergide and the appetite suppressants fenfluramine and dexfenfluramine. In addition, dopamine agonists used in the treatment of Parkinson disease and sleep disorders can also be ergot-derived, such as pergolide, cabergoline and bromocriptine, and can cause this form of fibrotic valvular disease. On the other hand, other dopamine agonists that are not ergot derived, such as ropinirole and pramipexole, have minimal or no affinity to 5-HT_{2B} receptors and do not cause valvular heart disease. Steiger et al⁴ conducted a systematic review of the literature to evaluate the risk of valvular heart disease associated with the use of dopamine agonists in Parkinson's disease. They demonstrated that the use of ergot-derived dopamine agonists (pergolide and cabergoline) was associated with increased risk whereas non-ergot agents did not cause this adverse effect.⁴

It is important to recognise this complication because although the use of serotonergic agents has declined for the treatment of migraine and for weight loss,⁵ they are still being used for other conditions such as Parkinson disease and restless leg syndrome, where the same pathology has been observed.⁴

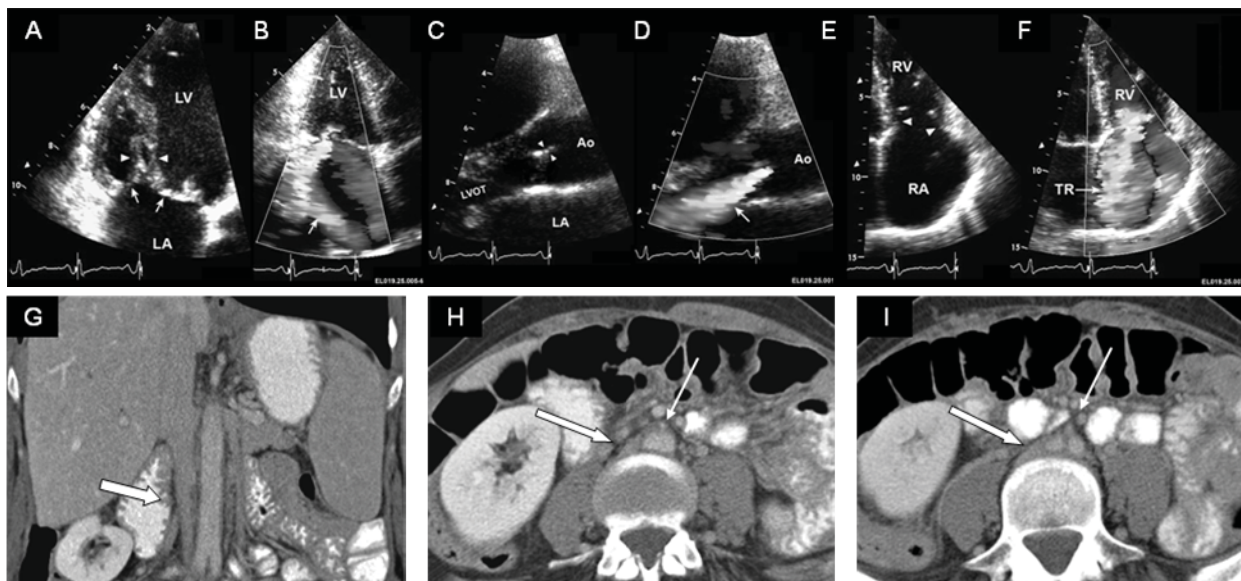


Fig. 1. (A) and (B). Echocardiography, apical 4 chamber view, systolic frames, focused on left ventricle (LV) and left atrium (LA). (A). Thickened mitral leaflets (arrows) and chordae (arrowheads) are evident on 2D imaging. (B). Colour flow imaging demonstrates severe mitral regurgitation (arrow) directed along lateral atrial wall (blue), and swirling around entire atrium, returning back toward mitral valve (red). (C) and (D). Echocardiography, parasternal long axis view, diastolic frames, focused on aortic valve cusps (arrowheads), left ventricular outflow tract (LVOT) and aortic root (Ao). (C). Valve cusps mildly thickened by 2D imaging. (D). Aortic regurgitation appears moderate by color flow imaging. LA = left atrium. (E) and (F). Apical 4 chamber view, systolic frames, focused on right ventricle (RV) and right atrium (RA). (E) Thickened tricuspid valve leaflets (arrowheads) are fixed in wide open position during systole. (F) Severe tricuspid regurgitation (arrow); colour flow fills the enlarged right atrium. (G). Coronal reformatted venous phase image from CT demonstrates tapered narrowing of the IVC in the lower abdomen (arrow). (H) and (I). Axial venous phase images from CT demonstrate narrowing of the IVC and right common iliac vein at the level of the aortic bifurcation (large arrows in H and I) and soft tissue encasement with narrowing of the inferior mesenteric artery (small arrows in H and I). The left common iliac vein is not visualised in (I).

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