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IMAGING

CASE REPORT: CLINICAL CASE

Minoxidil-Related Pericarditis

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ABSTRACT

This paper reports a case of a 53-year-old man presenting with recurrent pericardial effusions and one episode of pericarditis after short-term, low-dose minoxidil use, without prior kidney or heart failure history. The uniqueness lies in the rapid onset of a moderate pericardial effusion within 20 days, notably shorter than previously documented.
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HISTORY OF PRESENTATION

A 53-year-old man presented to an outside hospital after an abdominal ultrasound which incidentally showed a large pericardial effusion. He was asymptomatic and denied any recent illness. He was afebrile, had a heart rate of 102 beats/min, and had blood pressure of 132/85 mm Hg. He was euvolemic with normal cardiac examination revealing a non-displaced apical impulse, normal S_1 and S_2, and no murmurs, rubs, or gallops. He underwent pericardiocentesis and pericardial window and was discharged on colchicine 0.6 mg twice a day for 3 months with a diagnosis of idiopathic pericardial effusion. He presented 3 months later to an outside hospital with pleuritic chest pain; at that time he had just finished a 90-day course of colchicine 0.6 mg twice a day. He had an electrocardiogram with sinus tachycardia 110 beats/min and an elevated C-reactive protein of 11 mg/dL with serial high-sensitivity troponins <8 ng/L. He was hemodynamically stable, and physical examination was notable for a pericardial rub without signs of volume overload. He was diagnosed with idiopathic pericarditis and treated with ibuprofen 800 mg 3 times a day for 4 weeks followed by colchicine 0.6 mg twice a day for 3 months. He then presented to the Pericardial Disease Center at Cleveland Clinic for a second opinion 4 months later. At the time of evaluation, he had completed 4 weeks of nonsteroidal anti-inflammatory drugs and a 90-day course of colchicine 0.6 mg twice a day and was off therapy

TAKE-HOME MESSAGES

- Pericardial effusion is an adverse reaction to low-dose minoxidil use and can occur in patients without preexisting heart failure or renal insufficiency.
- Minoxidil-induced pericardial complications are unlikely to be dose-dependent and can occur rapidly after initiation of minoxidil. One must have a low index of suspicion for pericardial complications after low-dose minoxidil use regardless of duration of treatment.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

TTE = transthoracic echocardiogram

for a month. He was asymptomatic with an unremarkable physical examination.

PAST MEDICAL HISTORY

The patient's past medical history included presumed idiopathic pericardial effusion and pericarditis, well-controlled type 2 diabetes mellitus on metformin, and androgenetic alopecia.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included idiopathic or viral pericarditis, inflammatory pericarditis, drug-induced pericardial effusion, and other differentials of acute chest pain including acute coronary syndrome and pulmonary embolism.

INVESTIGATIONS

During his initial presentation to the outside hospital, laboratory testing included negative inflammatory markers, infectious work-up, and autoimmune work-up including antinuclear antibody, extractable nuclear antigen antibody panel, antineutrophil cytoplasmic antibodies, and rheumatoid factor were negative. A transthoracic echocardiogram (TTE) was done showing a moderate circumferential pericardial effusion (**Figure 1A**). He underwent pericardiocentesis with a pericardial window, and 1 L of transudative fluid was drained. Further fluid analysis had negative cytology and culture. During his second presentation to the outside hospital, he had an electrocardiogram with sinus tachycardia and an elevated C-reactive protein of 11 mg/dL with serial negative high-sensitivity troponins <8 ng/L. TTE at the time showed a large circumferential pericardial effusion (**Figure 1B**). He was diagnosed with idiopathic pericarditis and treated with ibuprofen 800 mg 3 times a day and colchicine 0.6 mg twice a day for 3 months. After presenting to the Pericardial Disease Center at Cleveland Clinic, repeat laboratory testing showed negative inflammatory markers, autoimmune and infectious work-up once again. On reviewing his medications, we noticed that he was started on minoxidil 5 mg once a day for hair growth 20 days prior to his initial presentation. Minoxidil was then discontinued with resolution of symptoms and effusion. A TTE 3 months after stopping minoxidil showed resolution of the pericardial effusion (**Figure 1C**) and a cardiac magnetic resonance (CMR) showed trivial pericardial late gadolinium enhancement and absence of pericardial edema and effusion on T2 short tau inversion recovery imaging (**Figures 1D and 1E**).

MANAGEMENT

Minoxidil was discontinued with serial TTE to assess for recurrence of the effusions and CMR to assess for presence of pericardial inflammation and edema. After ruling out autoimmune, infectious, and malignant etiologies and the resolution of the pericardial effusion with the cessation of the drug, we concluded that minoxidil was the most likely culprit in this patient's presentation.

OUTCOME AND FOLLOW-UP

A TTE 3 months after stopping minoxidil showed resolution of the pericardial effusion (**Figure 1C**), and a CMR showed trivial pericardial late gadolinium enhancement and absence of pericardial edema and effusion. He had no objective findings of disease recurrence and no symptoms or pleuritic chest pain on follow-up appointments.

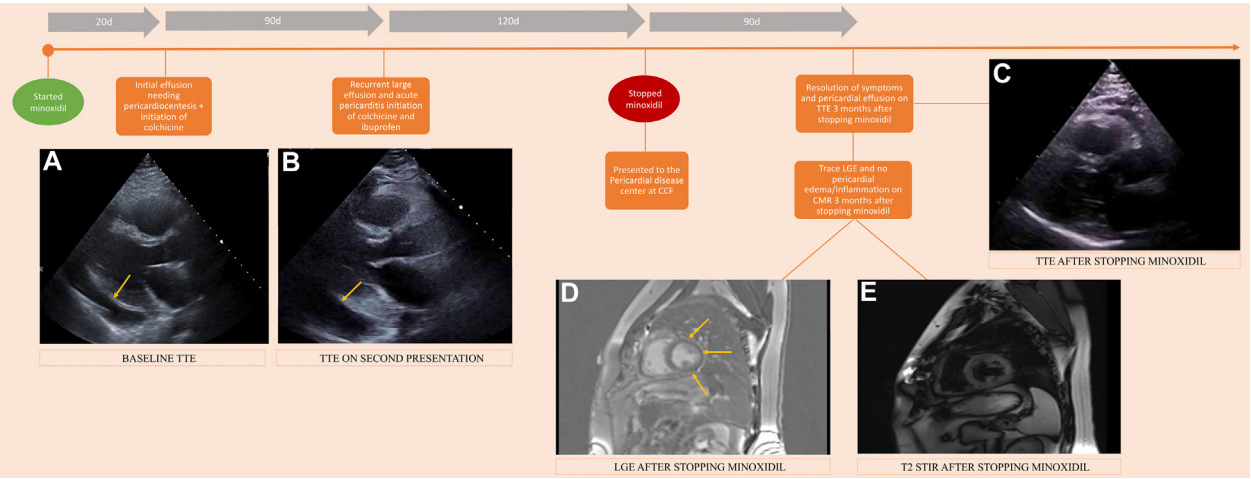
DISCUSSION

Minoxidil's mechanism of action includes directly acting on adenosine triphosphate-sensitive potassium channels in arteriolar smooth muscle causing vasodilation.[1] Its vasodilatory effect makes it beneficial in treating resistant hypertension not controlled by other guideline-directed therapy.[2] Minoxidil has been proven to be beneficial for hair growth when used at a low dose (< 5 mg) in patients with various forms of alopecia due to its vasodilatory effects and upregulation of vascular endothelial growth factor increasing cutaneous blood flow, oxygen, and growth factor delivery to the hair follicle.[3]

A few cases of minoxidil-induced pericardial effusion and subsequent tamponade have been published; however, these are mostly in patients with fluid overload including those with end-stage kidney disease or heart failure.[4-6] These patients have either used minoxidil at a higher dose (40 mg) for uncontrolled hypertension or were on chronic low-dose minoxidil (5 mg) for over 3 months.[4-6] It remains a rare phenomenon with a reported estimated incidence of 3%; however, that number is most likely an underestimate due to lack of pretreatment echocardiograms and attributing these effusions to other causes especially in the chronically ill patient populations.[7]

The proposed pathophysiology behind this idiosyncratic reaction is increased water and sodium retention due to augmented reabsorption in the proximal tubule and vasodilatory effect of the drug.[1] The patient exhibited no signs or symptoms of water retention or volume overload, challenging the

FIGURE 1 Timeline of Events



(A) TTE showing a moderate circumferential pericardial effusion (arrow). (B) TTE showing a large circumferential pericardial effusion with the peak pericardial effusion adjacent to posterior left ventricle measuring 3.86 cm (arrow). (C) Follow-up TTE 3 months after stopping minoxidil with resolution of pericardial effusion. (D) Follow-up CMR at the midventricle (papillary muscles) PSIR with trivial LGE. LGE shown by yellow arrows. (E) Follow-up CMR T2 STIR at the midventricle (papillary muscles) with no pericardial edema or thickening. CCF = Cleveland Clinic Foundation; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; PSIR = phase-sensitive inversion recovery; STIR = short inversion time inversion recovery; TTE = transthoracic echocardiogram.

prevailing theory that minoxidil-induced pericardial effusion and pericarditis is solely secondary to fluid retention. Instead, the adverse reaction may stem from a cardioselective mechanism specifically affecting cardiac tissue through direct interactions with receptors, signaling pathways, or cellular processes. This suggests a nuanced perspective that certain individuals may be predisposed to pericardial effusion development without the manifestation of a generalized systemic effect like fluid retention or volume overload. Another theory behind this idiosyncratic reaction is the increased expression of the sulfotransferase enzyme. Minoxidil is metabolized by follicular sulfotransferase into its active form, minoxidil sulfate. Patients with higher sulfotransferase activity had better hair-growth response than those with lower activity.[8] It would be interesting to investigate if increased sulfotransferase levels correlate with a predisposition to pericardial complications; however, this has not been studied previously. Understanding these precise mechanisms can lead to targeted therapeutic interventions, lead to preventative measures, and enhance risk stratification for individuals using minoxidil.

The causality between dosage and this reaction remains uncertain. However, the presence of cases associated with both low and high doses of minoxidil suggests a lack of dose-dependent relationships. The impact of titration strategies and treatment duration on the risk of pericardial effusion development with minoxidil has yet to be investigated. Moreover, the lack of pericardial effusion or pericarditis during extended minoxidil therapy does not eliminate the potential for these effects to manifest on reintroduction of the drug. A case by Lustig et al[9] illustrated a patient who had been using minoxidil for 8 years without complications who experienced pericarditis and pericardial effusion on resumption of minoxidil treatment after a 1-month drug-free interval.

Pericarditis typically occurs in patients taking minoxidil who have underlying systemic conditions (eg, uremia, viral infections, acute myocardial infarction).[4-6] Additionally, pericardial effusions commonly arise with prolonged minoxidil use, particularly in individuals with preexisting heart or kidney conditions. Here, we present a rare case of pericarditis and recurrent pericardial effusions after just 20 days of low-dose minoxidil use in a patient without prior history of heart or kidney disease, with other potential causes ruled out. We applied the validated Naranjo tool to assess the likelihood of minoxidil-induced reaction, yielding a score of 4, indicating plausible causality.[10] However, the inability to rechallenge the patient with the drug, along with the lack of drug-level measurements or drug-activating enzyme measurements, posed limitations because the patient moved to another state and became inaccessible. Large case-control studies

are necessary to provide a more comprehensive understanding of this relationship.

CONCLUSIONS

In this case, the patient developed recurrent pericardial effusions and one episode of pericarditis likely due to short-term low-dose use of minoxidil. The patient exhibited clinical improvement after cessation of minoxidil with follow-up imaging documenting objective resolution of pericardial inflammation and effusion. Patients on minoxidil should have routine evaluation for pericardial disease and a baseline TTE before initiation even in patients with no prior kidney or heart disease. Physicians should have a low index of suspicion for pericardial disease in patients on minoxidil regardless of dose or duration of treatment. Finally, we highlight the importance of multimodal imaging in diagnosis, management, and follow-up of pericardial effusions due to minoxidil toxicity in accordance with the most recent consensus statement highlighting the importance of multimodal imaging in the diagnosis, prognostication, and surveillance of pericardial diseases.[11]

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KEY WORDS cardiac magnetic resonance, echocardiography, pericardial effusion