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Evaluation of Pericardial Effusions in Alopecia Patients on Low-Dose Oral Minoxidil Therapy

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ABSTRACT

Background: Minoxidil is an anti-hypertensive vasodilator increasingly used off-label for the treatment of alopecia. It is associated with an increased risk of pericardial effusions, with recent reports even in patients on low-dose oral minoxidil (LDOM) therapy.
Objective: To evaluate whether LDOM is associated with increased prevalence of pericardial effusions in patients with alopecia.
Methods: In this cross-sectional study, point-of-care ultrasound was used to screen alopecia patients at dermatology appointments. Scans were evaluated by two independent cardiologists for the presence and size of effusions. The prevalence of effusions was compared between patients on LDOM therapy and patients not on minoxidil therapy.
Results: A total of 100 patients were evaluated for pericardial effusion: 51 LDOM patients and 49 control patients. The two groups were similar in terms of age (53.7 vs 54.1; *P*=0.91), sex (86% vs 73% female; *P*=0.14), and race. Small pericardial effusions (<1 cm) were identified in 5.8% of LDOM patients and 6% of control patients (*P*=1), none of which was symptomatic.
Limitations: This is a small, cross-sectional study with limitations on speculation of causality in confirmed cases.
Conclusion: We did not find evidence of increased prevalence of pericardial effusions in a small group of alopecia patients on LDOM.

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INTRODUCTION

Low-dose oral minoxidil (LDOM) is being increasingly prescribed off-label as an adjunct treatment for alopecia.[1] Historically, minoxidil has primarily been used as a treatment for severe, refractory hypertension due to its potent vasodilating properties. When prescribed at anti-hypertensive dosages (10–40mg daily), minoxidil is associated with pericardial effusions that may progress to cardiac tamponade, leading to an FDA-mandated black box warning.[2,3] Conversely, its side effect profile at low doses (up to 5 mg daily) in patients with alopecia has generally proven to be mild.[1] However, a recent report of anasarca and pericardial effusion developing shortly after initiating LDOM therapy in a healthy woman with frontal fibrosing alopecia has prompted concern within the dermatology community for potentially serious complications.[4] Additionally, two patients at our institution were incidentally diagnosed with pericardial effusions, prompting their care team to discontinue LDOM [NAM]. These findings raise the question of whether this now widely prescribed medication predisposes certain individuals to pericardial effusions even at the low dosages used for alopecia.

In this study, an association between LDOM therapy and pericardial effusions was evaluated by using ultrasound to compare the frequency of pericardial effusions in alopecia patients on LDOM therapy compared with those not on LDOM.

MATERIALS AND METHODS

Between January and April 2023, a sample of consecutive alopecia patients were imaged with non-diagnostic, ultrasound screening for pericardial effusions at an academic dermatology clinic.

For point-of-care ultrasound, the Terason uSmart 3300 (Teratech Corporation, Burlington, MA) ultrasound imaging system (version 5.14.4) was used throughout the entirety of the study. Patients were laid into a supine position and a subxiphoid window was obtained using a curved array transducer.[5] Ultrasound scans were independently evaluated for the presence and size of pericardial effusions by two board-certified cardiologists (IP, ED). Effusions were graded according to published guidelines. The largest diameter echo-free space between the visceral

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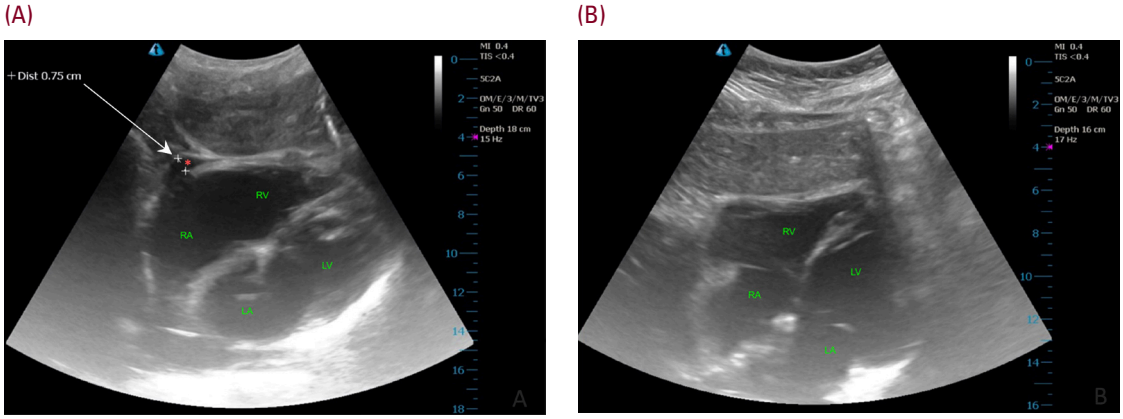
FIGURE 1. Evaluation of pericardial effusions in a subxiphoid view. (A) Example of a small effusion (red asterisk) measuring approximately 0.75 cm (white arrow). (B) Example of no effusion.



and parietal pericardium at end-diastole was measured and classified as trivial (only present during systole), small (<1 cm), moderate (1–2 cm), and large (>2 cm).[6] Trivial effusions are clinically insignificant and therefore were not considered as true effusions.[6] The frequency of all other pericardial effusions was compared between the LDOM and the control patients.

The results were analyzed in 2 groups, contingent on whether patients were on LDOM therapy continuously for >1 month. Controls were defined as any patients who were never prescribed or had not taken LDOM within one full month prior to the time of visit. Demographic information and primary hair loss diagnosis, stratified as either scarring (lichen planopilaris, frontal fibrosing alopecia, central centrifugal cicatricial alopecia) or non-scarring (alopecia areata, telogen effluvium, androgenetic alopecia, sebopsoriasis) were analyzed.

All statistical analysis was conducted using SPSS (version 29.0.0.0). Categorical variables were compared using Fisher's exact test while continuous variables were compared with Student's t-test.

RESULTS

A total of 100 patients were screened for pericardial effusion: 51 LDOM patients and 49 controls. The LDOM and control patients were similar in terms of age (53.7 vs 54.1 years old, respectively; *P*=0.91), sex (86% vs 73% female; *P*=0.14), and race (Table 1). The majority of patients treated with LDOM were either taking 2.5mg daily (70%) or 1.25 mg daily (21%). The mean treatment duration for patients on LDOM therapy was 11.8 months (SD 6.6)

Trivial effusions were found at similar rates in LDOM and control patients (35% in each group). A total of 3 patients were

TABLE 1.

Characteristics of Patients With Alopecia on Low-Dose Minoxidil Therapy Compared with Control Group

Variable	LDOM (n=51)	Control (n=49)	*P*-value
Age (years), mean (SD)	53.7 (16)	54.1 (18)	0.91
Treatment Duration (months), mean (SD)	11.8 (6.6)	n/a	
Sex			
Female	44 (86)	36 (73)	0.14
Male	7 (14)	13 (27)	
Alopecia Subtype			
Non-Scarring	32 (63)	41 (84)	0.02
Scarring	19 (37)	8 (16)	
Race			
White	40 (78)	36 (74)	0.64
Asian	6 (12)	5 (10)	1
Black or African American	2 (4)	0	0.49
Hispanic or Latino	0	3 (6)	0.11
Other or Mixed	3 (6)	5 (10)	0.48

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TABLE 2.

Comparison of Effusions Identified in LDOM Patients Compared with Control Patients			
Effusion Grade	LDOM (n=51)	Control (n=49)	*P*-value
Trivial	18 (35)	17 (35)	1
Small	3 (5.8)	3 (6.1)	1
Medium	0	0	1
Large	0	0	1

TABLE 3.

Patients Identified to Have Pericardial Effusions					
Age	Sex	Treatment	Race	LDOM Duration (months)	Relevant PMH
27	M	Control	white	n/a	none
57	F	Control	other or mixed	n/a	Atrial Fibrillation
67	F	Control	white	n/a	Parkinson's, Orthostatic Hypotension
54	F	2.5 mg LDOM	other or mixed	14.9	Myocardial Infarction, Hypothyroid
30	M	2.5 mg LDOM	other or mixed	15.2	none
86	F	1.25 mg LDOM	white	4.1	Breast cancer, status post lumpectomy, chemotherapy, radiation, Parkinson's

diagnosed with small pericardial effusions in each group. The age range of affected patients was 27 to 67 years old for controls and 30 to 86 years old for LDOM patients. Treatment duration did not appear to correlate with pericardial effusions in the LDOM group, as the mean treatment duration was 11.4 months for patients with effusions compared with 11.8 months overall in all LDOM-treated patients. None of the patients with pericardial effusions on imaging was symptomatic at the time of visit and none displayed any signs of fluid retention such as lower extremity edema.

DISCUSSION

To date, LDOM has generally demonstrated a mild side effect profile. The most commonly reported adverse effects at low doses are hypertrichosis and lower limb edema, both of which may be dose-dependent.[1,7] Cardiovascular adverse events are rare, with hypotension and tachycardia occasionally being reported.[1] Prior to two recent case reports of pericardial disease (ie, pericardial effusion and pericarditis), serious cardiac adverse events with LDOM had not been reported.[3,4] The emergence of these serious events warrants an assessment of whether prescribing a potent, direct peripheral vasodilator for alopecia may be associated with pericardial effusions.

The results of this small study ultimately did not demonstrate a difference in effusion rates in patients with alopecia treated with or without LDOM. Nearly all existing data on the association of minoxidil and pericardial effusions is from studies in patients with severe, refractory hypertension.[2,8,9] In this population, pericardial effusions have been described in approximately 3% of non-dialysis patients (n=1392), many of whom had comorbid congestive heart failure, renal dysfunction, or connective tissue disease,[2] all factors that can independently cause effusions.[10] The remaining patients without identifiable risk factors appeared to display fluid retention in the form of weight gain while on minoxidil.[11] Another study of 37 patients with hypertension treated with minoxidil identified effusions in 9 patients (24%).[9] A possible causal role of minoxidil in the development of the pericardial effusions was suggested as 5 patients had resolution of their effusions upon drug withdrawal, one of which was subsequently rechallenged and re-developed the effusion. It remains unclear whether the effusion resolution is dose-dependent, with one study[11] describing resolution with minoxidil dose reduction, while others report effusions resolving without minoxidil discontinuation.[2]

The mechanism by which minoxidil may cause pericardial effusions is largely unknown as none of the direct pharmacologic effects correlates with effusions.[9] Early studies of minoxidil at anti-hypertensive doses suggested that fluid retention (ie, weight gain) may be an early sign of underlying effusion.[2,11] Indeed, minoxidil's action as a direct arteriolar vasodilation permits fluid extravasation while activation of the renin-angiotensin-aldosterone system causes salt and water retention.[12] The result of these two mechanisms typically presents as lower limb edema. Theoretically, this may also cause dilation of epicardial capillaries, resulting in an imbalance of Starling forces.[11] However, our study did not find this to be a reliable sign as none of the patients with effusions demonstrated any peripheral edema or other signs of fluid retention. Additionally, 3 patients in

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the LDOM group reportedly had a history of minoxidil-induced lower extremity edema, though none of them had evidence of pericardial effusion at the time of screening.

We found approximately 6% of alopecia patients in both the LDOM and untreated groups to have small effusions at the time of evaluation. This was surprising as the original FDA warning (1980) suggests that pericardial effusions were present in 3% of hypertensive patients on minoxidil.[2,13] However, more recent studies of the general population have estimated the prevalence of pericardial effusions to be 6.5–9%, many of which were found in individuals who had no cardiovascular disease.[14,15] These discrepancies could be explained by differences in clinical setting, population studied, and methods used.[15]

Although the observed effusion rate was minimal, it is worth commenting on their clinical significance. When an effusion is detected, an assessment of its size, associated diseases, and hemodynamic impact dictates management.[15] Small, asymptomatic effusions are typically treated conservatively and only require minimal surveillance. Even large, chronic effusions are often managed conservatively if they are asymptomatic and are thought to be idiopathic.[10] The fear is that rapidly accumulating effusions can progress to tamponade and death, therefore requiring urgent pericardiocentesis. A wide range of processes involving the pericardium can result in effusion, including inflammation (eg, post-viral), injury (eg, post-myocardial infarction), or impaired lymphatic drainage (eg, congestive heart failure).[10] Other etiologies include autoimmune disease (eg, systemic lupus erythematosus), metabolic (eg, hypothyroidism), neoplastic, radiation, and uremia.[10,15] When encountered, patients with pericardial effusions should be worked up for one of these many possible underlying etiologies. In this study, two patients (both in the LDOM group) had underlying conditions that could have contributed to the development of pericardial effusions: one with a history of myocardial infarction and hypothyroidism, and one with a history of chest wall radiation (Table 3).

Limitations of this study include the cross-sectional nature which precludes speculation of causation. Additionally, conclusions on an association, or lack thereof, between LDOM and pericardial effusions are limited by this study's small sample size. The subxiphoid view was chosen in this study due to convenience for patients and the sonographer alike, however, additional views may be needed for an exhaustive assessment of effusions.

CONCLUSION

Low-dose oral minoxidil is a recent addition to the armamentarium of off-label alopecia treatments, though it has a long history as an anti-hypertensive agent with potentially serious side effects such as pericardial effusions.[13] The results of this small study did not find an increased prevalence of pericardial effusions in alopecia patients on LDOM therapy >1 month. Large, prospective studies are needed to confirm these findings and to speculate on possible mechanisms and patient risk factors. If these observations are substantiated, it may be that the pericardial disease described in recent reports is idiosyncratic. We were unable to determine the characteristics of patients with alopecia who are at greater risk of developing effusions. Out of an abundance of caution, providers should consider other risk factors for pericardial effusions (such as congestive heart failure and renal dysfunction) when initiating LDOM therapy. Patients who are incidentally found to have asymptomatic effusions may not necessarily require permanent discontinuation of minoxidil, but temporary discontinuation or dose reduction, along with workup by a cardiologist, is prudent.

DISCLOSURES

The authors have no conflicts to declare.

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