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Lower Limb Chronic Ischaemia Presenting Exclusively as Fungal Toenail Infection: Case Report and Brief Literature Review

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Abstract. *Background/Aim: Chronic lower limb ischaemia is a peripheral arterial disease (PAD) which is typically instigated by atherosclerotic plaques in the peripheral vasculature. This article reports on a unique case of chronic ischaemia in the lower limb, presenting in a distinctive manner as a fungal toenail infection. Case Report: An 82-year-old frail woman with multimorbidity presented with toenail symptoms in her right foot. While initial examination had shown onychomycosis, further investigation was unexpectedly consistent with chronic ischaemia in the lower limb. We explored the clinical presentation, diagnostic challenges encountered, and the subsequent management of this unique manifestation in the context of the patient's multimorbidity. Conclusion: This case report highlights the need to consider chronic limb ischaemia as a differential diagnosis in toenail infections when no alternative causes or predisposing factors are identified.*

Chronic lower limb ischemia, a form of peripheral arterial disease (PAD), commonly originates from atherosclerotic plaques within the peripheral blood vessels. It has been estimated that PAD affects 15-20% of individuals over 70 years old (1). Among individuals with PAD, only 22% exhibit symptoms, as reported in a study conducted across general practice centres (2). Moreover, among individuals diagnosed with lower limb PAD, it is estimated that only 30-40% present with claudication (3) and a significant portion (50%-90%) fail to report this symptom to their general practitioners (1). Consequently, missed diagnoses are common (2, 4). Herein, we discuss a case in which a patient's complaint regarding toenail issues prompted further investigation, ultimately uncovering chronic lower limb ischemia.

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Case Report

The patient is an 82-year-old woman weighing 78 kg, a former smoker (20-30 cigarettes/day for 20 years) and has a medical history including hypertension, hyperlipidaemia, and atrial fibrillation. The patient had undergone chemotherapy for breast cancer a few years earlier. Upon presentation, the patient complained of a persistent toenail infection on her right foot, which had been ongoing for several weeks (Figure 1). Initial examination revealed onychomycosis, characterised by superficial onycholysis with slight discolouration and plate disruption in the big and index toenails, resembling features of Candida infections. To confirm the suspected diagnosis of Candida infection, toenail clippings were collected for mycology analysis.

Since the patient did not have a history of immuno-suppression, diabetes, or renal failure, other potential factors contributing to fungal infections were explored. The absence of tight pain in the thigh or groin and the lack of rapid relief by elevation led to the exclusion of venous aetiology as a cause. The patient exhibited a slightly reduced sensation in her right foot and a weak dorsalis paedis pulse upon palpation. While the hyperaemic appearance of the patient's right foot compared to the left indicated adequate foot perfusion and initially ruled out ischemia, a red/purple-coloured foot can also signify microcirculation vasodilatation due to ischemia (4). The patient's mild eczema on the dorsal foot could also have contributed to the redness. The thickening of infected toenails and slight brittleness in the unaffected ones were suggestive of compromised circulation, prompting further investigation. The

patient's age, history of smoking, hypertension, and dyslipidaemia collectively serve as risk factors for PAD, which potentially made her more susceptible to fungal infections.

Further conversation with the patient uncovered that she struggled with walking and expressed that as "difficulty walking due to ageing" and "mild leg fatigue", which eased with rest while walking. Initially, the patient denied experiencing pain at rest or during sleep, as well as any foot numbness, attributing her discomfort solely to "leg fatigue", for which she had not sought medical advice. Additionally, the patient's son disclosed noticeable changes in her walking pattern with some weakness in her right leg due to age. Utilising the Edinburgh Claudication Questionnaire (5), intermittent claudication became evident. During the Buerger's test, observable venous guttering was also noted. Further assessment, including pulse palpation and evaluation of circulation and sensation in her lower limbs using Rutherford's classification for chronic limb ischemia, suggested inadequate arterial supply (classified as stage II on the Fontaine classification) (6). Consequently, a timely and appropriate referral was arranged.

While the patient did not appear to be facing immediate limb loss necessitating emergency endovascular intervention, a Doppler ultrasound study was deemed necessary to determine the extent of stenosis and identify sites of PAD (7). Subsequently, a diagnosis of chronic lower limb ischemia was confirmed. The specialist in secondary care concurred that there was no immediate risk of limb loss without emergency endovascular intervention and recommended conservative management. Notably, the patient's distal lesion did not exhibit alarming signs, such as ulceration, rest pain, or intolerable or sudden onset pain. The patient's pulses were also palpable, although weakly, and there were no notable decreases in muscular power or sensation.

Following confirmation through mycology culture, *Tinea unguium* was identified as the causative organism. As the infection had extended from the distal edge to encompass the entire toenail, oral antifungals were advised. Despite this recommendation, the patient expressed a preference for nail lacquer treatment. Consequently, Amorolfine nail lacquer was administered for 12 months with regular monitoring. However, even after this period, the onychomycosis persisted, and the initial symptoms resurfaced.

Figure 1. *The patient's right foot.*

Discussion

Onychomycosis constitutes more than half of all nail conditions in dermatology (8). Numerous documented factors may increase the likelihood of developing toenail fungal infections including iliofemoral deep vein thrombosis/ insufficiency (9, 10) and PAD (11, 12). Several risk factors for PAD exist, including but not limited to, age, smoking, hypertension, dyslipidaemia, and atrial fibrillation (13-16). These factors also increase the likelihood of rapid progression to critical limb or chronic limb-threatening ischemia (CLTI) (7, 17, 18). Key features of CLTI typically involve intolerable sudden-onset leg pain, non-palpable pulses, and significant reductions in muscular power or sensation (19). However, the weak dorsalis paedis pulse observed in some CLTI patients may be attributed to the collateral blood supply, which can be present in PAD (20), or erroneous pulse palpation, which is a common occurrence in about 20% of examinations conducted by non-specialists (21).

This case highlights the insidious nature of peripheral vascular disease with symptoms often attributed to ageing, and the need for clinicians assessing patients with suspected onychomycosis to look for underlying causes such as PAD by assessing the whole foot, which in this case identified asymptomatic PAD. Although fungal infections are known to affect up to 17% of the Swedish population (22), a small proportion will have secondary causes and early identification and management of occult PAD is important to prevent complications.

In patients diagnosed with PAD, the progression rate to CLTI is estimated to fall within the range of 7% to 30%, as indicated by one study (23), while a meta-analysis of 35 studies suggests it can reach as high as 21% (24). Given the narrow timeframe between the onset of hallmark CLTI symptoms and irreversible or extensive damage, which can be as brief as a few hours (25, 26), limb survival is always a priority as any delay or missed diagnosis could ultimately lead to limb amputation. Patients presenting with chronic limb ischemia at a later stage, as seen in this case, face the highest amputation rates, ranging from 12% to 67% over a span of four years (27). Prioritising patients with time-sensitive CLTI and promptly referring them for emergency endovascular intervention is crucial (23, 28) in order to mitigate the risk of amputation and decrease mortality rates (20).

The subsequent treatment goals for patients with PAD should focus on decreasing the occurrence of further cardiovascular events and enhancing mobility by addressing claudication symptoms and increasing walking distance (3, 29). Intermittent claudication, which is commonly observed in patients with more than 50% stenosis (1), remains a primary complication of PAD and significantly impairs the patient's quality of life. Evaluating the impact of PAD symptoms, including intermittent claudication, on quality of life can be determined using tools like the Vascular Quality of Life Questionnaire (30). While some patients may opt for conservative management, pharmacological interventions may be recommended for certain patients. For example, Cilostazol, known for its vasodilatory and antiplatelet as well as triglyceride-lowering effects with minimal adverse effects (31-34), has been shown to improve arterial foot perfusion and increase both pain-free and absolute claudication walking distances by 50%-67% (31, 35-38).

Conclusion

This case report highlights the variability in the presentation and severity of chronic limb ischemia, underscoring its consideration in patients with toenail infections where alternative causes are absent. Additionally, it notes that eczematous skin can obscure the paler colour of the foot in patients with PAD, and pulse palpation may not consistently rule out PAD.

Data Availability

All data relevant to the study are included in the article.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this case report.

Authors' Contributions

Manuscript discussion, writing, revision: KM, RD. Treatment of patients, data collection and assessment: KM, MA.

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References

1 Zeind CS, Carvalho MG: Applied therapeutics: the clinical use of drugs. Eleventh edition, 2018.
2 Stoffers HEJH, Rinkens PELM, Kester ADM, Kaiser V, Knottnerus JA: The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. Int J Epidemiol 25: 282-290, 1996.
3 Dhaliwal G, Mukherjee D: Peripheral arterial disease: Epidemiology, natural history, diagnosis and treatment. Int J Angiol 16(2): 36-44, 2007. DOI: 10.1055/s-0031-1278244
4 Lawrence M, Stephenson MJ, Al-Taan MO, McCarthy MMJ: Peripheral vascular disease. InnovAiT, 2010.
5 Lend GC, Fowkes FGR: The Edinburgh Claudication Questionnaire: An improved version of the WHO/Rose questionnaire for use in epidemiological surveys. J Clin Epidemiol 45: 1101-1109, 1992. DOI: 10.1016/0895-4356(92)90150-L
6 Hardman RL, Jazaeri O, Yi J, Smith M, Gupta R: Overview of classification systems in peripheral artery disease. Semin Intervent Radiol 31(4): 378-388, 2014. DOI: 10.1055/s-0034-1393976
7 Uccioli L, Meloni M, Izzo V, Giurato L, Merolla S, Gandini R: Critical limb ischemia: current challenges and future prospects. Vasc Health Risk Manag 14: 63-74, 2018. DOI: 10.2147/VHRM.S125065
8 del Rosso JQ: The role of topical antifungal therapy for onychomycosis and the emergence of newer agents. J Clin Aesthet Dermatol 7: 10-18, 2014.
9 Ozkan F, Ozturk P, Ozyurt K, İncİ MF, Kalender AM, Bakan B, Yuksel M: Frequency of peripheral arterial disease and venous insufficiency in toenail onychomycosis. J Dermatol 40(2): 107-110, 2013. DOI: 10.1111/1346-8138.12020
10 Shemer A, Nathansohn N, Kaplan B, Trau H: Toenail abnormalities and onychomycosis in chronic venous insufficiency of the legs: should we treat? Acad Dermatol Venereol 22(3): 279-282, 2008. DOI: 10.1111/j.1468-3083.2007.02401.x
11 Thomas J, Jacobson GA, Narkowicz CK, Peterson GM, Burnet H, Sharpe C: Toenail onychomycosis: an important global disease burden. J Clin Pharm Ther 35: 497-519, 2010. DOI: 10.1111/j.1365-2710.2009.01107.x
12 Gupta AK, Gupta MA, Summerbell RC, Cooper EA, Konnikov N, Albreski D, MacDonald P, Harris KA: The epidemiology of onychomycosis: possible role of smoking and peripheral arterial disease. J Eur Acad Dermatology Venereol 14(6): 466-469, 2000. DOI: 10.1046/j.1468-3083.2000.00124.x
13 Fowkes FGR, Housley E, Cawood EHH, Macintyre CCA, Ruckley CV, Prescott RJ: Edinburgh artery study: Prevalence of

asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 20(2): 384-392, 1991. DOI: 10.1093/ije/20.2.384

14 Sentí M, Nogués X, Pedro-Botet J, Rubiés-Prat J, Vidal-Barraquer F: Lipoprotein profile in men with peripheral vascular disease. Role of intermediate density lipoproteins and apoprotein E phenotypes. Circulation 85(1): 30-36, 1992. DOI: 10.1161/01.CIR.85.1.30

15 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR: Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 45 Suppl S: S5-67, 2007. DOI: 10.1016/j.jvs.2006.12.037

16 Willigendael EM, Teijink JAW, Bartelink ML, Kuiken BW, Boiten J, Moll FL, Büller HR, Prins MH: Influence of smoking on incidence and prevalence of peripheral arterial disease. J Vasc Surg 40: 1158-1165, 2004. DOI: 10.1016/j.jvs.2004.08.049

17 Stoffers HE, Kester AD, Kaiser V, Rinkens PE, Knottnerus JA: Diagnostic value of signs and symptoms associated with peripheral arterial occlusive disease seen in general practice. Med Decis Making 17(1): 61-70, 1997. DOI: 10.1177/0272989X9701700107

18 Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A, Hirsch AT: Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. J Vasc Surg 60(3): 686-695.e2, 2014. DOI: 10.1016/j.jvs.2014.03.290

19 Duff S, Mafilios MS, Bhounsule P, Hasegawa JT: The burden of critical limb ischemia: a review of recent literature. Vasc Health Risk Manag 15: 187-208, 2019. DOI: 10.2147/VHRM.S209241

20 Conte MS, Bradbury AW, Wang S: Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg 58: S1-S109.e33, 2019. DOI: 10.1016/j.ejvs.2019.05.006

21 Brearley S, Shearman CP, Simms MH: Peripheral pulse palpation: an unreliable physical sign. Ann R Coll Surg Engl 74: 169-171, 1992

22 Özenci V, Klingspor L, Ullberg M, Chryssanthou E, Denning DW, Kondori N: Estimated burden of fungal infections in Sweden. Mycoses 62(11): 1043-1048, 2019. DOI: 10.1111/MYC.12981

23 Henke PK: Contemporary Management of acute limb ischemia: Factors associated with amputation and in-hospital mortality. Semin Vasc Surg 22(1): 34-40, 2009. DOI: 10.1053/j.semvascsurg.2009.01.002

24 Sigvant B, Lundin F, Wahlberg E: The risk of disease progression in peripheral arterial disease is higher than expected: A meta-analysis of mortality and disease progression in peripheral arterial disease. Eur J Vasc Endovasc Surg 51(3): 395-403, 2016. DOI: 10.1016/j.ejvs.2015.10.022

25 McNally MM, Univers J: Acute limb ischemia. Surg Clin North Am 98(5): 1081-1096, 2018. DOI: 10.1016/j.suc.2018.05.002

26 Campbell WB, Ridler BMF, Szymanska TH: Current management of acute leg ischaemia: results of an audit by the vascular surgical society of Great Britain and Ireland. Br J Surg 85(11): 1498-1503, 2003. DOI: 10.1046/j.1365-2168.1998.00906.x

27 Reinecke H, Unrath M, Freisinger E, Bunzemeier H, Meyborg M, Luders F, Gebauer K, Roeder N, Berger K, Malyar NM: Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. Eur Heart J 36(15): 932-938, 2015. DOI: 10.1093/eurheartj/ehv006

28 Gray BH, Sullivan TM: Vascular claudication: How to individualize treatment. Cleve Clin J Med 64, 1997.

29 Martone VD, Perna S, Cacciatore F, Corrado S, di Donato A, di Iorio A, Brevetti G: Intermittent claudication and risk of cardiovascular events. Angiology 49(9): 843-848, 1998. DOI: 10.1177/000331979804900908

30 Nordanstig J, Wann-Hansson C, Karlsson J, Lundström M, Pettersson M, Morgan MB: Vascular Quality of Life Questionnaire-6 facilitates health-related quality of life assessment in peripheral arterial disease. J Vasc Surg 59(3): 700-707.e1, 2014. DOI: 10.1016/j.jvs.2013.08.099

31 Thompson PD, Zimet R, Forbes WP, Zhang P: Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol 90(12): 1314-1319, 2002. DOI: 10.1016/S0002-9149(02)02869-2

32 Elam MB, Heckman J, Crouse JR, Hunninghake DB, Herd JA, Davidson M, Gordon IL, Bortey EB, Forbes WP: Effect of the novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication. Arterioscler Thromb Vasc Biol 18(12): 1942-1947, 1998. DOI: 10.1161/01.ATV.18.12.1942

33 Mohler ER, Beebe HG, Salles-Cuhna S, Zimet R, Zhang P, Heckman J, Forbes WP: Effects of cilostazol on resting ankle pressures and exercise-induced ischemia in patients with intermittent claudication. Vasc Med 6(3): 151-156, 2001. DOI: 10.1177/1358836X0100600305

34 Woo SK, Kang WK, Kwon K: Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. Clin Pharmacol Ther 71(4): 246-252, 2002. DOI: 10.1067/mcp.2002.122474

35 Dawson DL, Cutler BS, Hiatt WR, Hobson RW, Martin JD, Bortey EB, Forbes WP, Strandness D: A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 109(7): 523-530, 2000. DOI: 10.1016/S0002-9343(00)00569-6

36 Dawson DL, Cutler BS, Meissner MH, Strandness DE: Cilostazol has beneficial effects in treatment of intermittent claudication. Circulation 98(7): 678-686, 1998. DOI: 10.1161/01.CIR.98.7.678

37 Money SR, Herd J, Isaacsohn JL, Davidson M, Cutler B, Heckman J, Forbes WP: Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. J Vasc Surg 27(2): 267-275, 1998. DOI: 10.1016/S0741-5214(98)70357-X

38 Thompson PD, Zimet R, Forbes WP, Zhang P: Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol 90(12): 1314-1319, 2002. DOI: 10.1016/S0002-9149(02)02869-2

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