REVIEW ARTICLE

CUTANEOUS HEMOSIDEROSIS IN CHRONIC VENOUS INSUFFICIENCY: A REVIEW

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Abstract

Hemosiderosis is the deposition of hemosiderin, a storage form of iron derived from the breakdown of erythrocytes. This process commonly occurs in patients with chronic venous insufficiency (CVI) due to venous hypertension and vascular ectasia. Cutaneous accumulation of hemosiderin in CVI causes brown hyperpigmentation and contributes to lipodermatosclerosis and ulceration, further highlighting the pathogenic role of iron metabolism in these disorders. In this review, we examine the pathophysiology and clinical presentation of hemosiderosis in CVI, summarize its management and prevention strategies, and explore its impact on quality of life.

INTRODUCTION

Chronic venous insufficiency (CVI) is a common disorder that affects millions of Americans.[1] Clinical manifestations can vary in severity from varicose veins, which may be viewed as a cosmetic concern, to venous ulcers, which can greatly impact quality of life. Skin changes that are common in CVI include edema, dermatosclerosis, eczema and pigmentation.[2] The Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification system is widely used to describe the clinical range of manifestations (C1–C6) with the following categories: C1) telangiectasias or reticular veins; C2) varicose veins; C3) edema; C4) changes in skin and subcutaneous tissue secondary to chronic venous disease, which is then subcategorized into C4a) pigmentation or eczema, C4b) lipodermatosclerosis and C4c) corona phlebectatica; C5) healed ulcer; and C6) active venous ulcer.[3]

Hemosiderin is a storage form of iron, which is derived from the breakdown of erythrocytes.[4] Both melanin and hemosiderin are seen in dermal histiocytes and contribute to the observed CVI-related pigmentation. However, hemosiderin is believed to play an important role in the evolution toward the more severe CVI-related skin changes, such as lipodermatosclerosis and ulceration.[5,6] Thus, diligent prevention and management of hemosiderosis-related skin changes in CVI is critical to avoid the progression of disease and to improve patients' quality of life.

Literature search and data sources

PubMed was searched on February 20, 2021, for each of the following terms separately: "cutaneous hemosiderosis," "hemosiderosis," "iron metabolism," "chronic venous insufficiency," "chronic venous insufficiency treatment," "chronic venous insufficiency quality of life," "venous leg ulcers," "lipodermatosclerosis," "stasis dermatitis" and "hyperpigmentation."

PATHOPHYSIOLOGY

CVI is characterized by incompetent valves, which lead to reflux and venous hypertension. Chronic reflux increases pressure in the veins, which further worsens valve insufficiency and perpetuates a cycle of venous dilation.[7] Enlarged intercellular spaces from increased venous pressure allow extravasation of erythrocytes into the perivascular spaces, termed erythrodiapedesis.[8] Lysed dermal erythrocytes release hemoglobin, ferritin and hemosiderin.[9] Stromal hemosiderin deposition over time, as well as an increased production of melanin in the epidermis, is thought to cause hyperpigmentation in CVI.[10] One study found that all biopsies taken from pigmented discolored skin of limbs with varicose veins showed a higher content of melanin in the epidermis compared to controls, while stromal hemosiderin was found mostly in the severely pigmented skin areas of lipodermatosclerosis.[5]

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Hemosiderin deposition into dermal stroma may also contribute to venous ulcer pathogenesis. Typically, the accumulation of hemosiderin deposits and iron-laden macrophages is visualized within the wound bed of chronic venous ulcers (Figures 1A–1C). In contrast, there is a decrease in hemosiderin and erythrocyte extravasation associated with venous ulcer healing.[11,12] Some authors suggest that hemosiderin deposits are involved in the pathogenesis of venous ulcers through the generation of reactive oxygen species (ROS).[12–14] ROS can lead to persistent inflammation, excessive production of matrix metalloproteases (MMPs), increased connective tissue degradation, lipid peroxidation and ulcer formation.[13] This ongoing state of oxidative stress may also prevent ulcer healing.[14] Iron release may be directly involved with the hyperexpression of MMPs,[11] although it is normally controlled by the ferritin-ferroxidase system. This system is usually effective in preventing the activation of this cascade. Of significance, the HFE ("High Iron [Fe]") gene mutation that encodes for human homeostatic iron regulator protein is the most recognized genetic defect in iron metabolism. Therefore, it has been proposed that a HFE gene mutation could also be present in patients with CVI ulcers.[9] One study found that C282Y mutation of the HFE gene had significantly increased the risk of ulcer formation in primary chronic venous disease by more than sixfold.[9]

FIGURE 1A:
Reactive proliferation of capillary lobules in upper dermis with underlying dermal fibrosis with perivascular chronic inflammation (H&E 5x)

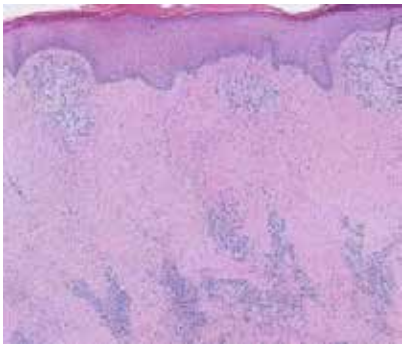


FIGURE 1B:
Same field demonstrating stromal hemosiderin deposits highlighted with blue cellular uptake (Prussian blue 5x)

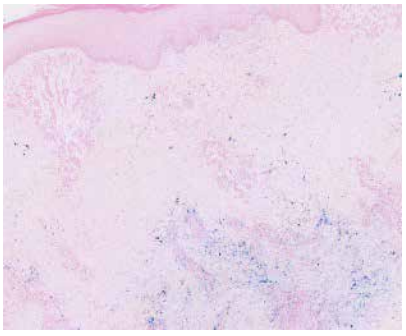
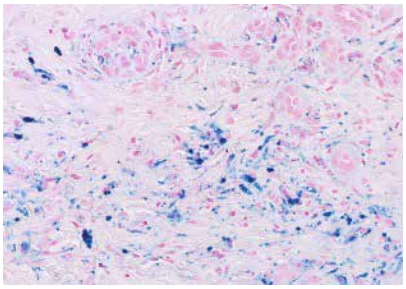


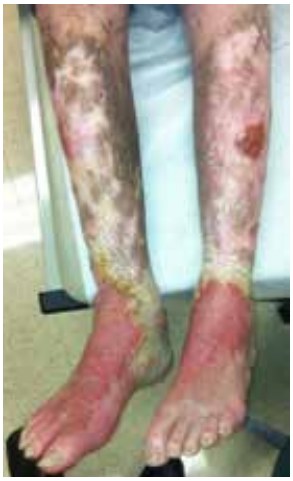
FIGURE 1C:
Numerous hemosiderophages highlighted with iron stain by showing cytoplasmic blue staining uptake (30x of iron stain (Prussian Blue))



CLINICAL MANIFESTATIONS

Pigmentation in CVI is typically located on the lower medial third of the lower leg but can involve the entire gaiter area. It can manifest in several ways, such as small patches of mild dyschromia or as extensive skin darkening.[5] A variety of skin changes associated with hyperpigmentation can occur in CVI, including stasis dermatitis, xerosis and lipodermatosclerosis (Figure 2). Stasis dermatitis is the cutaneous inflammation observed in CVI, which presents with erythematous, scaling, eczematous plaques that are most commonly located in the area of the ankle.[15,16] Acute forms may be associated with pruritus and can present with vesicles, weeping plaques, crusting and fissuring.

FIGURE 2:
Lower extremities demonstrating atrophie blanche, hemosiderosis, stasis dermatitis, venous ulceration and severe lipodermatosclerosis



Stasis dermatitis can progress to lipodermatosclerosis, a chronic form of fibrosing panniculitis associated with CVI that is characterized by induration, cutaneous thickening, loss of tensile strength, and hyperpigmentation (Figure 3).[17] Lipodermatosclerosis is a sclerotic tightening of the soft tissues that can lead to a band/tourniquet-like constriction of the ankle region and has been classically described as an inverted "champagne bottle" appearance (Figure 4).[17] The "acute" form of lipodermatosclerosis refers to painful erythema, which can mimic cellulitis, although this visibly subsides with leg elevation (Figure 5).[18] A slower onset of lipodermatosclerosis manifests over weeks to months and is typically associated with a bilateral leg presentation and a lack of warmth and edema, leading to a favorable diagnosis of lipodermatosclerosis over cellulitis.[18]

FIGURE 3:
Bilateral lower extremities with lipodermatosclerosis and hemosiderosis

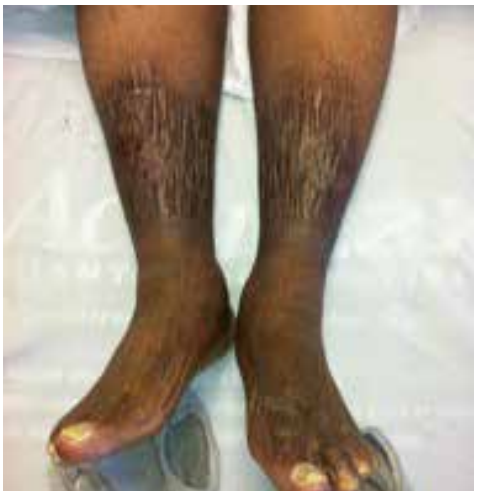
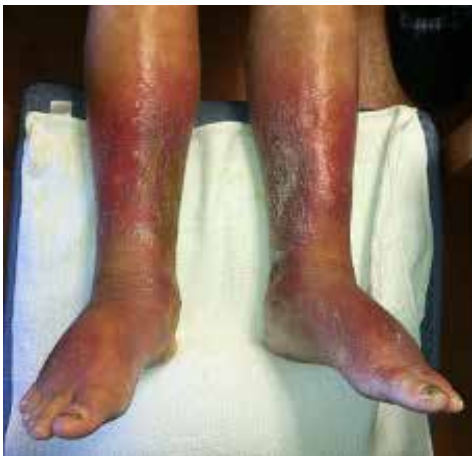


FIGURE 4:
Left lower extremity demonstrating severe lipodermatosclerosis—the "inverted champagne bottle shape" with hemosiderosis

FIGURE 5:
Bilateral lower extremities with acute lipodermatosclerosis, mimicking cellulitis



EFFECTS ON QUALITY OF LIFE

More severe manifestations of CVI include lower extremity edema, hemosiderosis and ulcerations. CVI may also cause significant pain, depression, sleep disturbance and discomfort. All of these factors can lead to a decreased quality of life (QoL).[19] A study of 1893 patients with CVI found that this disease had a significant negative impact on physical, psychological and the social functioning components on QoL.[20] A decrease in QoL was correlated with increasing severity of CVI based on CEAP classification.[20] CVI symptoms can also impact one's ability to perform activities of daily living (ADLs), such as standing for a long time, putting on shoes, climbing stairs, carrying heavy loads, and performing housework.[21] One study found that women were more likely than men to report their effect on ADLs due to CVI.[21]

Additionally, a large study of 16,251 patients including both sexes with venous disease found that the presence of leg symptoms, such as tiredness, heaviness and pain, positively correlated with the worsening of visible findings that included telangiectasia, varicose veins, edema, and ulcers.[22] The correlation between these leg symptoms and the visible signs of disease was more marked in women than men, suggesting that women may be more negatively impacted by CVI-related skin changes than men.[22] Despite the chronic nature of CVI, one study found that patients with a higher CEAP class were more likely to seek emergency care services for CVI-related symptoms, including heaviness in the legs, pain and swelling, suggesting that there is a greater physical, emotional, and financial burden on patients with more advanced skin disease.[23] The visual nature of hemosiderosis may also have a negative impact on self-confidence and self-esteem. Additionally, the use of continuous compression therapy can further contribute to unsightliness and discomfort, particularly in the summer months.

MANAGEMENT AND PREVENTION

No specific therapies have been established to target the problem of hemosiderosis in CVI. Treatment of skin hyperpigmentation often requires a multi-therapy approach that involves in-office procedures.[24] While bleaching agents, such as topical hydroquinone, are the mainstay therapy for hypermelanosis, hemosiderosis is thought to be unresponsive to bleaching agents.[25] However, intense pulsed light and lasers have been reported to successfully treat hyperpigmentation in CVI.[26,27] Effective management of hemosiderosis involves treating the underlying venous hypertension and chronic stasis induced dermatitis. Conservative measures such as compression therapy, skin care, leg elevation and exercise are first-line measures for the treatment of CVI.[28] Skin changes induced by chronic venous stasis, such as skin darkening and lichenification, may be significantly reversed with application of systematic compression, in addition to preventing chronic stasis effects. Patients with this condition require education on the importance of daily use of compression garments due to the fundamental effect of this measure in slowing the progression of disease and potentially reversing the cutaneous changes.

Patients who have persistent symptoms and documented superficial venous reflux may benefit from a referral to a vascular

specialist to consider more invasive vascular procedures, such as radiofrequency endovenous thermal ablation, vein stripping, phlebectomy, or sclerotherapy. Patients with acute stasis dermatitis usually benefit from a high- or mid-potency topical corticosteroids once or twice daily for 1–2 weeks over affected skin.[16] Simultaneous compression therapy is crucial in management. A short course of systemic corticosteroids may also be considered in patients who do not respond to topical steroids, or who have secondary allergic contact dermatitis.[16]

Although no substantial treatment evidence exists regarding cutaneous hemosiderosis, there is significant evidence that oral pentoxifylline facilitates healing time in stasis-induced leg ulcers.[29] The mechanism of action has been attributed to the reduction in blood viscosity and vascular permeability when administered orally at 400 mg three times daily for a range of 2–3 months, as either monotherapy or in combination with compression.[29] Research also indicates that oral pentoxifylline at higher dosage (800 mg three times daily) may be more beneficial in chronic leg ulcers.[30] However, gastrointestinal intolerance may preclude the treatment at a higher dose. As cutaneous hemosiderosis can be a sequela of increased vascular permeability, oral pentoxifylline may be an additional useful management option.

Given the progressive nature of hemosiderosis, its prevention is key to reducing the disease burden. Initiation of CVI treatment at its early stages (CEAP 1–3: telangiectasias, varicose veins, and/or edema) is paramount. Lifestyle changes to prevent venous ulcers should be implemented in patients with CVI, both with and without hyperpigmentation. Such interventions include minimizing prolonged standing, elevating legs, compression hosiery, weight loss, avoiding local trauma, and seeking medical care when the skin is damaged.[31] Proposed risk factors for the development of first-time venous leg ulcers may include: a family history of CVI of maternal origin, a history of deep vein thrombosis, multiple pregnancies, occupational exposures and history of strenuous exercise.[31]

CONCLUSION

CVI is an extremely common disorder with a variety of dermatologic manifestations. Cutaneous hemosiderosis is a pathogenic mechanism seen in CVI, contributing to the development of hyperpigmentation, stasis dermatitis, lipodermatosclerosis, and potentially venous ulceration through the generation of ROS. Cutaneous hemosiderosis is disfiguring, can greatly affect quality of life, and may increase the use of emergency care services. The first-line treatment to avoid hemosiderosis and to reduce its progression is preventive measures, including compression therapy, lifestyle modifications and early medical interventions.

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REFERENCES

1. Surowiec. SKPSM. Venous Insufficiency. StatPearls Publishing. 2020.
2. Garg N, Gloviczki P. Chapter 55 - Chronic Venous Insufficiency. In: Creager MA, Beckman JA, Loscalzo J, eds. *Vascular Medicine: A Companion to Braunwald's Heart Disease* (Second Edition). W.B. Saunders; 2013: 652–666.
3. Lurie F, Passman M, Meisner M, *et al*. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord*. 2020;8(3):342–352. doi:10.1016/j.jvsv.2019.12.075
4. Boes KM, Durham AC. Chapter 13 - Bone Marrow, Blood Cells, and the Lymphoid/Lymphatic System. In: Zachary JF, ed. *Pathologic Basis of Veterinary Disease (Sixth Edition)*. Mosby; 2017:724–804.e2.
5. Caggiati A, Rosi C, Franceschini M, Innocenzi D. The nature of skin pigmentations in chronic venous insufficiency: A preliminary report. *Eur J Vasc Endovasc Surg*. 2008/01/01/ 2008;35(1):111–118. doi:10.1016/j.ejvs.2007.08.007
6. Caggiati A, Rosi C, Casini A, *et al*. Skin iron deposition characterises lipodermatosclerosis and leg ulcer. *Eur J Vasc Endovasc Surg*. 2010;40(6):777–782. doi:10.1016/j.ejvs.2010.08.015
7. Ligi D, Croce L, Mannello F. Chronic venous disorders: The dangerous, the good, and the diverse. *Int J Mol Sci*. 2018;19(9):2544. doi:10.3390/ijms19092544
8. Wenner A, Leu HJ, Spycher M, Brunner U. Ultrastructural changes of capillaries in chronic venous insufficiency. *Pathobiology*. 1980;48(1):1–14. doi:10.1159/000162969
9. Zamboni P, Izzo M, Tognazzo S, *et al*. The overlapping of local iron overload and HFE mutation in venous leg ulcer pathogenesis. *Free Radic Biol Med*. 2006;40(10):1869–1873. doi:10.1016/j.freeradbiomed.2006.01.026
10. Chacon AH, Morrison B, Hu S. Acquired hemochromatosis with pronounced pigment deposition of the upper eyelids. *J Clin Aesthet Dermatol*. 2013;6(10):44–46. PMID: 24155994
11. Zamboni P, Scapoli G, Lanzara V, *et al*. Serum iron and matrix metalloproteinase-9 variations in limbs affected by chronic venous disease and venous leg ulcers. *Dermatol Surg*. 2005;31(6):644–649. doi:10.1111/j.1524-4725.2005.31611
12. Herrick SE, Sloan P, McGurk M, Freak L, McCollum CN, Ferguson MW. Sequential changes in histologic pattern and extracellular matrix deposition during the healing of chronic venous ulcers. *Am J Pathol*. 1992;141(5):1085–1095. PMID: 1279979
13. Wenk J, Foitzik A, Achterberg V, *et al*. Selective pick-up of increased iron by deferoxamine-coupled cellulose abrogates the iron-driven induction of matrix-degrading metalloproteinase 1 and lipid peroxidation in human dermal fibroblasts in vitro: a new dressing concept. *J Invest Dermatol*. 2001;116(6):833–839. doi:10.1046/j.1523-1747.2001.01345.x
14. Yeoh-Ellerton S, Stacey MC. Iron and 8-isoprostane levels in acute and chronic wounds. *J Invest Drmatol*. 2003;121(4):918–925. doi:10.1046/j.1523-1747.2003.12471.x
15. Sundaresan S, Migden MR, Silapunt S. Stasis dermatitis: Pathophysiology, evaluation, and management. *Am J Clin Dermatol*. 2017;18(3):383–390. doi:10.1007/s40257-016-0250-0
16. Fransway AF. Stasis dermatitis. UpToDate. Updated August 26, 2019. Accessed February 20, 2021.
17. Miteva M, Romanelli P, Kirsner RS. Lipodermatosclerosis. *Dermatol Ther*. 2010;23(4):375–388. doi:10.1111/j.1529-8019.2010.01338.x
18. Hirschmann JV, Raugi GJ. Lower limb cellulitis and its mimics: part II. Conditions that simulate lower limb cellulitis. *J Am Acad Dermatol*. 2012;67(2):177–186. doi:10.1016/j.jaad.2012.03.023
19. Edwards H, Finlayson K, Skerman H, *et al*. Identification of symptom clusters in patients with chronic venous leg ulcers. *J Pain Symptom Manage*. 2014;47(5):867–875. doi:10.1016/j.jpainsymman.2013.06.003
20. Branisteanu DE, Feodor T, Baila S, Mitea IA, Vittos O. Impact of chronic venous disease on quality of life: Results of vein alarm study. *Exp Ther Med*.

2019;17(2):1091–1096. doi:10.3892/etm.2018.7054

21. Chiesa R, Marone EM, Limoni C, Volonté M, Schaefer E, Petrini O. Effect of chronic venous insufficiency on activities of daily living and quality of life: correlation of demographic factors with duplex ultrasonography findings. *Angiology*. 2007;58(4):440–449. doi:10.1177/0003319706292012
22. Chiesa R, Marone EM, Limoni C, Volontè M, Petrini O. Chronic venous disorders: correlation between visible signs, symptoms, and presence of functional disease. *J Vasc Surg*. 2007;46(2):322–330. doi:10.1016/j.jvs.2007.04.030
23. Ruggiero M, Grande R, Naso A, *et al*. Symptoms in patients with skin changes due to chronic venous insufficiency often lead to emergency care service: An Italian observational study. *Int Wound J*. 2016;13(5):967–971. doi:10.1111/iwj.12498
24. Desai SR. Hyperpigmentation therapy: a review. *J Clin Aesthet Dermatol*. 2014;7(8):13–17. PMID: 25161755
25. Parsi K. Dermatological manifestations of Venous Disease: Part I. 2007.
26. Pimentel CL, Rodriguez-Salido MJ. Pigmentation due to stasis dermatitis treated successfully with a noncoherent intense pulsed light source. *Dermatol Surg*. 2008;34(7):950–951. doi:10.1111/j.1524-4725.2008.34184.x
27. Wu DC, Goldman MP. Successful treatment of chronic venous stasis hyperpigmentation of the lower limbs with the picosecond alexandrite laser. *Dermatol Surg*. 2018;44(6):881–883. doi:10.1097/dss.0000000000001333
28. Gloviczki P, Comerota AJ, Dalsing MC, *et al*. The care of patients with varicose veins and associated chronic venous diseases: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011;53(5 Suppl):2s–48s. doi:10.1016/j.jvs.2011.01.079
29. Jull AB, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. *Cochrane Database Syst Rev*. 2012;12(12):Cd001733. doi:10.1002/14651858.CD001733.pub3
30. Falanga V, Fujitani RM, Diaz C, *et al*. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: Efficacy in a randomized, placebo-controlled trial. *Wound Repair Regen*. 1999;7(4):208–213. doi:10.1046/j.1524-475x.1999.00208.x
31. Brown A. Life-style advice and self-care strategies for venous leg ulcer patients: What is the evidence? *J Wound Care*. 2012;21(7):342–350. doi:10.12968/jowc.2012.21.7.342