

Asymptomatic Cutaneous Polyarteritis Nodosa: Treatment Options and Therapeutic Guidelines



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PRACTICE POINTS

- Cutaneous polyarteritis nodosa should be in the differential of new-onset livedo reticularis.
- Workup with biopsy and specific blood work is important.
- Treatment options at this time are limited.

Cutaneous polyarteritis nodosa (CPAN) is a rare cutaneous small- to medium-vessel vasculitis of unknown etiology. Clinically it ranges in manifestation from livedo reticularis to large cutaneous ulcers and necrosis. Prognosis is favorable and progression to systemic polyarteritis nodosa is rare. There are multiple treatment options, none of which have proven to be definitively effective. Cutaneous polyarteritis nodosa has been associated with abnormal antibody testing with elevations of antiphospholipid cofactor antibody, lupus anticoagulant, anticardiolipin antibody, and anti- β_2 -glycoprotein I-dependent cardiolipin antibodies, as well as elevated anti-phosphatidylserine-prothrombin complex antibody. These antibodies suggest increased risk for thrombosis and systemic diseases such as lupus or other autoimmune connective tissue disease. We present a case of asymptomatic CPAN and evaluate if treatment should be instituted for asymptomatic disease that presents with abnormal antibody findings.

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In 1931, Lindberg¹ described a cutaneous variant of polyarteritis nodosa, which lacked visceral involvement and possessed a more favorable prognosis.² Cutaneous polyarteritis nodosa (CPAN) is a localized small- to medium-vessel vasculitis restricted to the skin. Both benign and chronic courses have been described, and systemic involvement does not occur.³ Diagnostic criteria proposed by Nakamura et al³ in 2009 included cutaneous nodules, livedo reticularis, purpura, or ulcers; histopathologic

fibrinoid necrotizing vasculitis of small- to medium-sized vessels; and exclusion of systemic symptoms (eg, fever, hypertension, weight loss, renal failure, cerebral hemorrhage, neuropathy, myocardial infarction, ischemic heart disease, pericarditis, pleuritis, arthralgia/myalgia). Nodules occur in 30% to 50% of cases and can remain for years if left untreated. Ulcerations occur in up to 30% of patients. Myositis, arthritis, and weakness also have been reported with this condition.⁴ Cutaneous polyarteritis nodosa has been associated with abnormal antibody testing with elevations of antiphospholipid cofactor antibody, lupus anticoagulant, anticardiolipin antibody, and anti- β_2 -glycoprotein I-dependent cardiolipin antibody, as well as elevated anti-phosphatidylserine-prothrombin complex antibody.⁵ These antibodies suggest increased risk for thrombosis and systemic diseases such as lupus or other autoimmune connective tissue disease. The distinction of this entity from systemic polyarteritis nodosa is key when determining treatment options and monitoring parameters.

Case Report

A 66-year-old woman was referred to our facility by an outside dermatologist with a mildly pruritic, blanchable, reticulated erythema on the chest and bilateral arms and legs of 3 months' duration consistent with livedo reticularis (Figure 1). Prior systemic therapy included prednisone 10 mg 3 times daily, fexofenadine, loratadine, and hydroxyzine. When the systemic steroid was tapered, the patient developed an asymptomatic flare of her eruption. On presentation, the lesions had waxed and waned, and the patient was taking only vitamin B₁₂ and vitamin C. Her medical history was notable for an unknown-type lymphoma of the chest wall diagnosed at 46 years of age that was treated with an unknown chemotherapeutic agent, chronic pancreatitis that resulted in

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a duodenectomy at 61 years of age, chronic cholecystitis, and 1 first-trimester miscarriage. Outside laboratory tests, including a comprehensive metabolic panel, complete blood cell count, urinalysis, renal function, and liver function tests were within reference range, except for the finding of mild leukocytosis (11,000/ μ L)(reference range, 3800–10,800/ μ L), which resolved after steroids were discontinued, with otherwise normal results. Punch biopsy of a specimen from the right thigh revealed medium-vessel vasculitis consistent with polyarteritis nodosa (Figure 2). Laboratory workup by our facility including hepatitis panel, perinuclear antineutrophil cytoplasmic antibody, cytoplasmic antineutrophil cytoplasmic antibody, factor V Leiden, prothrombin time/international normalized ratio, anticardiolipin antibody, and proteins C and S were all within reference range. Abnormal values included a low positive but nondiagnostic antinuclear antibody screen with negative titers, and the lupus anticoagulant titer was mildly elevated at 44 IgG binding units (reference range, <40 IgG binding units). Serum protein electrophoresis (SPEP) and urine protein electrophoresis also were performed, and SPEP was low positive for elevated κ and γ light chains. The patient was referred to oncology, and further testing revealed no underlying malignancy. The patient was monitored and no treatment was initiated; her rash completely resolved within 3 months. Laboratory monitoring at 6 months including SPEP, urine protein electrophoresis, lupus anticoagulant, and clotting studies all were within reference range.

Comment

Although the treatment of systemic polyarteritis nodosa often is necessary and typically involves high-dose corticosteroids and cyclophosphamide, the treatment of CPAN initially is less aggressive. Of the options available for treatment of CPAN, each has associated risks and side effects. Chen⁶ classified CPAN into 3 groups: 1 (mild), 2 (severe with no systemic involvement), and 3 (severe with progression to systemic disease)(Table). The authors performed a review of all the published treatments and their respective side effects to evaluate if treatment should be instituted for asymptomatic (group 1) disease presenting with abnormal antibody findings as demonstrated in our case.

First-line treatment of CPAN includes nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine.⁷ Nonsteroidal anti-inflammatory drugs are preferred; however, they also have been associated with gastrointestinal tract upset and increased risk for peptic ulcer disease with long-term use. Although colchicine often is used in conjunction with NSAIDs⁸ for its anti-inflammatory activity, no studies have been performed on this drug as monotherapy, and the side effect of diarrhea often limits its use.

Other therapies include dapsone, which should be monitored carefully due to the risk for dapsone hypersensitivity syndrome.^{8,9} Topical corticosteroids have been proven effective for mild cases of confluent erythema

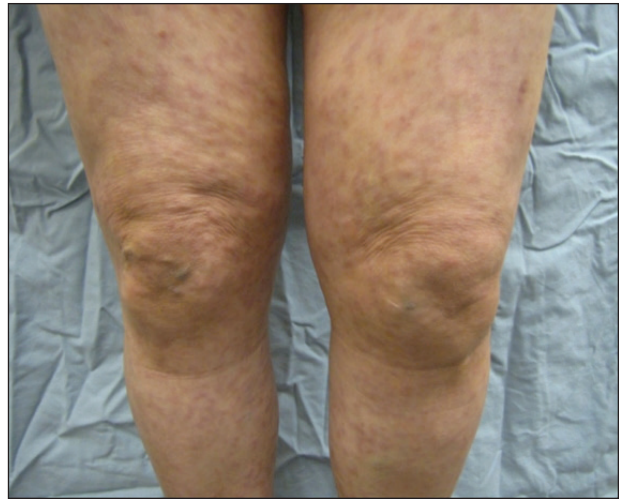


FIGURE 1. Livedo reticularis on the legs.

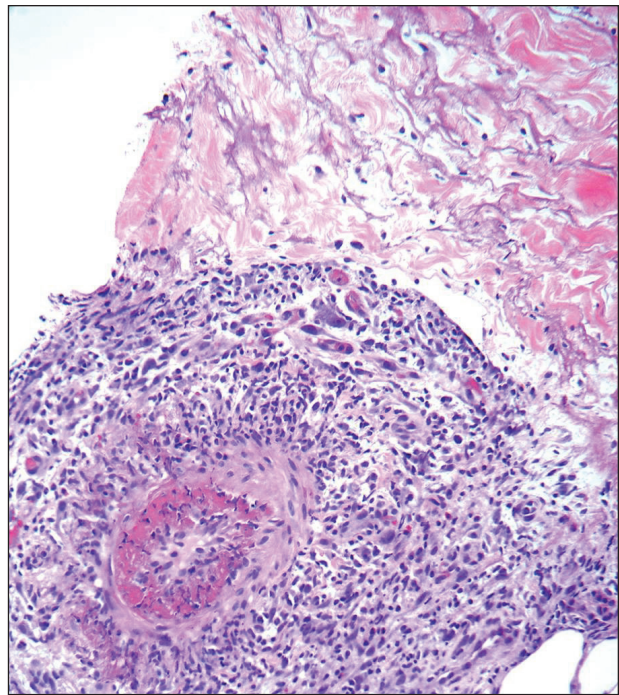


FIGURE 2. Medium-vessel vasculitis with a lymphocytic infiltrate around a medium-sized vessel (H&E).

with remission occurring as early as 4 weeks.⁴ Some reports emphasize the role of streptococcal infections in CPAN, especially in children.^{8,10-12} Consequently it is recommended that anti-streptolysin O titers should be included in the workup for CPAN. Long-term penicillin prophylaxis and tonsillectomy have been used to prevent disease flares with limited success.^{8,10-12}

For more severe disease, especially with neuromuscular involvement, oral methylprednisolone up to 1 mg/kg daily

CPAN Classification

Group Number	Clinical Findings
1 (mild cutaneous)	Disease confined to skin with occasional involvement of peripheral nerves, skeletal muscles of extremities; benign course (16 cases)
2 (severe)	Disease limited to skin, muscle, peripheral nerves; no progression to visceral involvement over 5- and 11-year follow-up (2 cases)
3 (progressive)	Beginning with cutaneous lesion and progressing to the systemic form after 18 and 19 years of recurring cutaneous lesions (2 cases); positive ANA and RF ^a

Abbreviations: CPAN, cutaneous polyarteritis nodosa; ANA, antinuclear antibody; RF, rheumatoid factor.

^aOne patient died of gastrointestinal tract bleeding.

Data from Chen.⁶

has been used and has proven effective in the control of acute exacerbations.^{7,13} However, the many adverse effects of systemic steroids limit their use long-term, and taper will often result in flare of disease.^{4,7} Medications used in conjunction with steroids include hydroxychloroquine, dapsone, azathioprine, cyclophosphamide, methotrexate, sulfapyridine, pentoxifylline, infliximab, etanercept, and intravenous immunoglobulin.^{4,9,12-17}

Low-dose methotrexate has shown some improvement in skin disease with CPAN, but other case reports suggest that complete remission is not achieved with this drug.^{15,18} More studies are needed to assess the use of methotrexate for CPAN.

Immunomodulators have been used in multiple case reports with varying levels of success. Rogalski and Sticherling⁴ reported 3 cases that cleared with methylprednisolone plus azathioprine ranging from 4 weeks to 6 months; nausea limited tolerance of azathioprine in 1 case. Mycophenolate mofetil also was successfully used in 2 cases with clearance at 17 weeks and 6 months. In this series of cases, cyclosporine was ineffective for CPAN.⁴ Two case reports documented cutaneous clearance with cyclophosphamide in conjunction with prednisolone.^{9,10} No prospective trials have been performed on these medications, and immunosuppressants should only be considered in steroid-resistant cases.

The use of intravenous immunoglobulin has been reported effective in prior cases that showed resistance to more conventional trials of steroids, azathioprine, and/or cyclophosphamide.^{12,14} Intravenous immunoglobulin may be regarded as a treatment option for severe resistant disease. Several case reports also have documented success using tumor necrosis factor α blockers, particularly infliximab, as an adjunct to steroids and etanercept as both a steroid adjunct and monotherapy.^{16,17,19} More studies are necessary to evaluate these treatments.

Additionally, single case reports have outlined the use of other therapeutic agents, including tamoxifen

(10 mg twice daily increased to 20 mg twice daily during episodes of breakthrough lesions),²⁰ hyperbaric oxygen therapy (100% oxygen for 90 minutes 5 times weekly at 1.5 atm absolute followed by 2 weeks of 2 atm absolute),²¹ and granulocyte-macrophage colony-stimulating factor (300 μ g injection in small portion to ulcer edges twice monthly for 2 months).²² All of these treatments show promise, but data are limited.

Because thrombosis is postulated to be a potential mechanism leading to CPAN, agents such as pentoxifylline, clopidogrel, and warfarin have been examined as treatment options. Pentoxifylline in combination with mycophenolate mofetil has been successful in treating a case that was resistant to other immunosuppressants.²³ Clopidogrel blocks the adenosine diphosphate pathway and impairs clot retraction. Clopidogrel was reported effective in an acute flare of CPAN for clearance of skin lesions and normalization of lupus anticoagulant.²⁴ It also was used successfully in recurrent CPAN after steroid treatments in a patient with neuromuscular symptoms. There was no recurrence in either of the patients in this case report series. Warfarin therapy at an international normalized ratio of 3.0 also has demonstrated success in halting disease progression and in facilitating the resolution of skin changes and normalization of anti-phosphatidylserine-prothrombin complex antibodies.²⁴ Our review of the literature did not reveal evidence of a standardized length of treatment following symptom resolution or if treatment is indicated in asymptomatic disease, or as in our case, with only mild elevations of antiphospholipid antibodies.

Conclusion

Multiple treatment options exist for CPAN, but the data on their efficacies is limited and based only on anecdotal evidence, not prospective analysis. We believe that it seems reasonable to initiate treatment only for symptomatic disease or cases in which the antibody titers suggest that the

patient may be at high risk for thrombosis. Mild symptoms and mild cutaneous changes would suggest the likely choice of NSAIDs, colchicine, or dapsone as treatment options versus no treatment. In patients with antibody titers, pentoxifylline, clopidogrel, or warfarin may be considered first-line therapies. With severe ulcerative lesions and neuromuscular involvement, steroids, immunosuppressants, and other investigative agents should be contemplated. In our patient, the laboratory studies were repeated and normalized on complete resolution of her livedo eruption. She remained asymptomatic and clear for 8 months without any treatment. The incidence of this presentation of CPAN is unknown and is likely underreported, as we would not expect most patients to present to their physicians for the evaluation of otherwise asymptomatic livedo reticularis. In essence, our case report suggests that it may be prudent to simply monitor patients with asymptomatic CPAN.

REFERENCES

- Lindberg K. Ein Beitrag zur Kenntnis der Periarteritis nodosa. *Acta Med Scand.* 1931;76:183-225.
- Kraemer M, Linden D, Berlit P. The spectrum of differential diagnosis in neurological patients with livedo reticularis and livedo racemosa [published online August 26, 2005]. *J Neurol.* 2005; 252:1155-1166.
- Nakamura T, Kanazawa N, Ikeda T, et al. Cutaneous polyarteritis nodosa: revisiting its definition and diagnostic criteria. *Arch Dermatol Res.* 2009;301:117-121.
- Rogalski C, Sticherling M. Panarteritis cutanea benigna—an entity limited to the skin or cutaneous presentation of a systemic necrotizing vasculitis? report of seven cases and review of the literature. *Int J Dermatol.* 2007;46:817-821.
- Kawakami T, Yamazaki M, Mizoguchi M, et al. High titer of anti-phosphatidylserine-prothrombin complex antibodies in patients with cutaneous polyarteritis nodosa. *Arthritis Rheum.* 2007;57:1507-1513.
- Chen KR. Cutaneous polyarteritis nodosa: a clinical and histopathological study of 20 cases. *J Dermatol.* 1989;6:429-442.
- Morgan AJ, Schwartz RA. Cutaneous polyarteritis nodosa: a comprehensive review. *Int J Dermatol.* 2010;49:750-756.
- Ishiguro N, Kawashima M. Cutaneous polyarteritis nodosa: a report of 16 cases with clinical and histopathologic analysis and review of the published work. *J Dermatol.* 2010;37:85-93.
- Flanagan N, Casey EB, Watson R, et al. Cutaneous polyarteritis nodosa with seronegative arthritis. *Rheumatology (Oxford).* 1999;38:1161-1162.
- Fathalla B, Miller L, Brady S, et al. Cutaneous polyarteritis nodosa in children. *J Am Acad Dermatol.* 2005;53:724-728.
- Misago N, Mochizuki Y, Sekiyama-Kodera H, et al. Cutaneous polyarteritis nodosa: therapy and clinical course in four cases. *J Dermatol.* 2001;28:719-727.
- Breda L, Franchini S, Marzetti V, et al. Intravenous immunoglobulins for cutaneous polyarteritis nodosa resistant to conventional treatment. *Scand J Rheumatol.* 2016;45:169-170.
- Maillard H, Szczesniak S, Martin L. Cutaneous periarteritis nodosa: diagnostic and therapeutic aspects of 9 cases. *Ann Dermatol Venereol.* 1999;26:125-129.
- Lobo I, Ferreira M, Silva E. Cutaneous polyarteritis nodosa treated with intravenous immunoglobulin. *J Eur Acad Dermatol Venereol.* 2007;22:880-882.
- Boehm J, Bauer R. Low-dose methotrexate controls a severe form of polyarteritis nodosa. *Arch Dermatol.* 2000;136:167-169.
- Campanilho-Marques R, Ramos F, Canhão H, et al. Remission induced by infliximab in a childhood polyarteritis nodosa refractory to conventional immunosuppression and rituximab. *Joint Bone Spine.* 2014;81:277-278.
- Inoue N, Shimizu M, Mizuta M, et al. Refractory cutaneous polyarteritis nodosa: successful treatment with etanercept. *Pediatr Int.* 2017;59:751-752.
- Schartz NE. Successful treatment in two cases of steroid dependent cutaneous polyarteritis nodosa with low-dose methotrexate. *Dermatology.* 2001;203:336-338.
- Valor L, Monteagudo I, de la Torre I, et al. Young male patient diagnosed with cutaneous polyarteritis nodosa successfully treated with etanercept. *Mod Rheumatol.* 2014;24:688-689.
- Cvancara JL, Meffert JJ, Elston DM. Estrogen sensitive cutaneous polyarteritis nodosa: response to tamoxifen. *J Am Acad Dermatol.* 1998;39:643-646.
- Mazokopakis E, Milkas A, Tsartsalis A, et al. Improvement of cutaneous polyarteritis nodosa with hyperbaric oxygen. *Int J Dermatol.* 2009;48:1017-1029.
- Tursen U, Api H, Kaya TI, et al. Rapid healing of chronic leg ulcers during perilesional injections of granulocyte-macrophage colony stimulating factor in a patient with cutaneous polyarteritis nodosa. *J Eur Acad Dermatol Venereol.* 2006;20:1341-1343.
- Kluger N, Guillot B, Bessis D. Ulcerative cutaneous polyarteritis nodosa treated with mycophenolate mofetil and pentoxifylline. *J Dermatolog Treat.* 2011;22:175-177.
- Kawakami T, Soma Y. Use of warfarin therapy at a target international normalized ratio of 3.0 for cutaneous polyarteritis nodosa. *J Am Acad Dermatol.* 2010;63:602-606.