

# Acrocyanosis After Immunotherapy: Vasculitis or Vasculopathy?

**Authors:** \*Yuliya Lytvyn,<sup>1</sup> Megan E. Himmel,<sup>2</sup> Carrie Ye,<sup>3</sup> Jarek Szlichta,<sup>4</sup> Shahin Jamal,<sup>5,6</sup> Alexandra Saltman<sup>2</sup>

1. Division of Dermatology, Department of Medicine, University of Toronto, Canada
  2. Division of Rheumatology, Department of Medicine, University of Toronto, Canada
  3. Division of Rheumatology, Department of Medicine, University of Alberta, Edmonton, Canada
  4. Department of Electrical Engineering and Computer Science, York University, Toronto, Canada
  5. Division of Rheumatology, University of British Columbia, Vancouver, Canada
  6. Arthritis Research Canada, Vancouver, Canada
- \*Correspondence to Julia.lytvyn@mail.utoronto.ca

**Disclosure:** The authors have declared no conflicts of interest.

**Keywords:** Cancer immunotherapy, digital ischemia, immune checkpoint inhibitor (ICI), oncology, rheumatic immune related adverse event, vasculitis.

**Citation:** Dermatol AMJ. 2025;2[1]:35-36.  
<https://doi.org/10.33590/dermatolamj/OEWI8118>

literature.<sup>1-14</sup> Integrating the findings, they propose a hypothetical pathogenesis and approach to treatment.

## RESULTS

In comparison to previously reported cases, the CanRIO cases had earlier onset after ICI exposure (median: 6 weeks versus 10 weeks), were mostly seronegative (33% versus 63%), and were treated more aggressively with a combination of immunosuppression, vasodilation, and antiplatelet agents (triple therapy). Angiography in all cases did not find evidence of proximal vasculitis; distal imaging uniformly showed small vessel occlusion, but no vasculitis. All CanRIO cases that received triple therapy had either stabilization or resolution of cyanosis, while management with separate therapies led to poorer outcomes. There were no amputations in the CanRIO group, where 5/10 in the literature that were not managed by triple therapy required amputation.

## BACKGROUND AND AIMS

Acral digital ischemia associated with immune checkpoint inhibitor (ICI) use is a rare and poorly understood toxicity.

## METHODS

The authors report eight cases of acral digital ischemia post-ICI from the Canadian Research Group of Rheumatology in Immuno-Oncology (CanRIO) retrospective cohort between 2017–2023, and compare them to the existing 14 reported cases in the

## CONCLUSION

Acral digital necrosis is a rare immune-related adverse event associated with ICI therapy, with unknown pathogenesis or optimal treatment. The eight cases from CanRIO were identified early and received aggressive “triple therapy” with resolution of cyanosis, contrasting with previously reported cases. The authors hypothesize that ICI-associated acral digital necrosis is a new iatrogenic disease triggered by an underlying inflammatory vasculopathy with distal vessel occlusion, leading to ischemia and requiring early initiation of vasodilation and antiplatelet/anticoagulant therapy.

## References

1. Thoreau B et al. Acute lower limb ischaemia and diabetes in a patient treated with anti-PD1 monoclonal antibody for metastatic melanoma. *Acta Derm Venereol.* 2017;97(3):408-9.
2. Gambichler T et al. Paraneoplastic acral vascular syndrome in a patient with metastatic melanoma under immune checkpoint blockade. *BMC Cancer.* 2017;17(1):327.
3. Le Burel S et al. Onset of connective tissue disease following anti-PD1/PD-L1 cancer immunotherapy. *Ann Rheum Dis.* 2018;77(3):468-70.
4. Padda A et al. Ipilimumab induced digital vasculitis. *J Immunother Cancer.* 2018;6(1):12.
5. Comont T et al. Immune checkpoint inhibitor-related acral vasculitis. *J Immunother Cancer.* 2018;6(1):120.
6. Khaddour K et al. Acral vascular necrosis associated with immune-check point inhibitors: case report with literature review. *BMC Cancer.* 2019;19(1):449.
7. Franco F et al. Nivolumab-associated digital small-vessel vasculitis in a patient with an advanced renal cell carcinoma. *Immunotherapy.* 2019;11(5):379-84.
8. Reijers ILM et al. Acrocyanosis after neoadjuvant ipilimumab plus nivolumab: a case report. *Clin Exp Rheumatol.* 2020;38(5):1031-2.
9. Zenati N et al. [Digital ischaemia with fingertip ulcers during ipilimumab therapy]. *Ann Dermatol Venereol.* 2020;147(3):212-6. (In French).
10. O'Connor P et al. Acral vascular syndrome during an immune checkpoint inhibitor. *BMJ Case Rep.* 2020;13(5):e233463. Erratum in: *BMJ Case Rep.* 2021;14(2):e233463corr1.
11. Grand J et al. An unusual case of digital cyanosis. *J Am Coll Cardiol.* 2022;79(Suppl 9):3292.
12. Thomas A et al. Pembrolizumab-associated acral necrosis and esophageal necrosis. *Curr Probl Cancer Case Rep.* 2022;8(1):100193.
13. Kefas J et al. Small vessel vasculitis and dry gangrene secondary to combined CTLA-4 and PD-1 blockade in malignant mesothelioma. *BMC Rheumatol.* 2022;6(1):10.
14. Yerolatsite M et al. Digital ischemia: a rare immune-related adverse event of immune checkpoint inhibitors - case report and review of the literature. *Rheumatol Int.* 2024;44(12):3141-49.