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Reactive Angioendotheliomatosis with Atypical Features Following Immune Checkpoint Inhibitor Therapy: A Diagnostic Challenge

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HIGHLIGHTS

- Rare palmoplantar vascular lesions
- Atypical endothelial proliferation
- Strong CD31 positivity
- Possible nivolumab association
- Improvement with conservative treatment

Key Words:

Reactive angioendotheliomatosis
Nivolumab
Immune checkpoint inhibitors
Palmoplantar lesions
Immunohistochemistry

ABSTRACT

Introduction: Reactive angioendotheliomatosis is a rare, benign cutaneous vascular proliferation that may mimic malignant vascular disorders. Atypical endothelial morphology can complicate diagnosis, particularly in patients receiving anticancer therapy. This case highlights an unusual palmoplantar presentation following nivolumab administration and the importance of clinicopathological correlation. **Case Presentation:** A 65-year-old woman with colonic adenocarcinoma diagnosed three years earlier, receiving FOLFOX chemotherapy and nivolumab, presented with progressively enlarging, tender, erythematous palmoplantar plaques of 20 days' duration. The lesions appeared approximately three weeks after a nivolumab cycle. Examination revealed firm, non-blanching plaques, some progressing to well-defined ulcers with purulent, exudative bases. Histopathology demonstrated complete epidermal denudation and proliferation of thin blood vessels in the upper and mid dermis, lined by cells with plump nuclei. Luminal formation was indistinct in some areas, and neutrophilic infiltration of sweat glands was absent. Immunohistochemistry showed strong CD31 positivity in arborizing vascular channels and low Ki-67 positivity. Differential diagnoses included Kaposi sarcoma, spindle cell hemangioma and angiosarcoma. Integrated assessment supported reactive angioendotheliomatosis with atypical features, with endothelial atypia interpreted as treatment-related. Conservative management comprised an emollient, topical antibiotics, oral antihistamines and an oral analgesic. At two weeks, the palmar and plantar lesions had significantly improved. **Results:** Histopathology and immunohistochemistry supported a diagnosis of reactive angioendotheliomatosis with atypical features, with strong CD31 positivity and low Ki-67 expression. The palmoplantar lesions showed significant clinical improvement after two weeks of conservative treatment. **Conclusion:** Reactive angioendotheliomatosis should be considered when atypical vascular lesions arise during anticancer therapy. Clinical findings, histopathology, immunohistochemistry and lesion evolution require integrated interpretation to distinguish reactive proliferation from malignant mimics. The temporal relationship with nivolumab suggested a possible association but did not establish causality, particularly with concurrent chemotherapy and underlying malignancy. Continued clinical follow-up remains important.



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INTRODUCTION

Reactive angioendotheliomatosis (RAE) is a rare, benign cutaneous vascular disorder characterised by proliferation of endothelial cells within and around dermal blood vessels. It generally occurs in association with an underlying systemic condition and presents with variable manifestations, including erythematous or violaceous patches, indurated plaques, purpura, nodules, and occasionally painful ulceration or necrosis [1]. This clinical heterogeneity can obscure recognition and create substantial overlap with inflammatory, infectious, thrombotic, and neoplastic disorders. Although the vascular proliferation itself is benign, its appearance may indicate an important underlying disease requiring investigation [2].

The pathogenesis of RAE remains incompletely understood, but vascular occlusion and consequent tissue hypoxia are considered important mechanisms [3]. Reduced tissue perfusion may stimulate angiogenic signalling, promoting reactive proliferation of endothelial cells and pericytes. Reported associations include peripheral vascular disease, autoimmune disorders, infections, and haematological abnormalities. Histopathological examination typically demonstrates dermal capillary proliferation, intravascular endothelial hyperplasia, & sometimes microthrombi, usually without significant cytological atypia. Endothelial markers, including CD31 and CD34, support vascular differentiation; however, their expression alone cannot establish the benign nature of a lesion [4].

Immune checkpoint inhibitors have transformed cancer treatment by enhancing antitumour immune responses through blockade of inhibitory immune pathways. However, this immune activation can also produce cutaneous adverse events with diverse clinical and histopathological patterns. Documented manifestations include maculopapular eruptions, lichenoid dermatitis, psoriasiform reactions, and autoimmune blistering disease. Consequently, new skin lesions arising during immunotherapy require careful assessment to distinguish treatment-associated inflammation from unrelated dermatoses, infection, or malignancy. The diversity of these reactions makes clinicopathological correlation particularly important when the presentation does not resemble a recognised toxicity pattern [5].

RAE with atypical features presents an additional diagnostic challenge because unusual clinical findings or concerning microscopic appearances may raise suspicion of angiosarcoma, Kaposi sarcoma, or intravascular lymphoma [6]. Importantly, endothelial marker positivity does not exclude angiosarcoma, and apparently reactive findings must be interpreted alongside lesion evolution and the broader clinical context. A reported case of metastatic angiosarcoma initially resembling RAE illustrates the potential consequences of diagnostic overlap and the value of reassessment when clinical behaviour and histology are discordant [2].

The present report examines RAE with atypical features arising following immune checkpoint inhibitor therapy, highlighting the diagnostic uncertainty encountered in this setting. A temporal

relationship warrants consideration of a possible treatment association but does not independently establish causality. The report emphasises integrated clinical assessment, histopathological evaluation, appropriate immunohistochemistry, and consideration of alternative systemic triggers to support accurate diagnosis and informed management decisions.

CASE PRESENTATION

A 65-year-old woman presented to the dermatology clinic with a 20-day history of progressively enlarging, tender, erythematous plaques predominantly involving the palms and soles. She had been diagnosed with adenocarcinoma of the colon three years earlier and was receiving FOLFOX chemotherapy and nivolumab. The skin lesions first appeared approximately three weeks after a cycle of nivolumab. On examination, the plaques were firm and non-blanching, with dimensions ranging from 0.5×0.5 cm to 1×2 cm. Some lesions had developed into well-defined, tender ulcers with a purulent, exudative base. The clinical photographs demonstrated palmar plaques with overlying yellow crusts and ulcerative lesions affecting the soles. Thus, the presenting cutaneous changes included both plaques and ulcers in a patient undergoing treatment for colonic adenocarcinoma. The history of recent nivolumab administration accompanied the progressive development of these painful lesions, which formed the principal dermatological presentation at the time of clinical assessment (**Figure 1**).

Histopathological examination demonstrated complete denudation and absence of the epidermis (**Figure 2 & 3**). The upper and mid dermis showed proliferation of thin blood vessels lined by cells with plump nuclei. Luminal formation was not identifiable in some areas. No evidence of neutrophilic infiltration of the sweat glands was observed. Immunohistochemical examination showed strong CD31 positivity within the arborizing vascular channels, while Ki-67 demonstrated low positivity. The microscopic assessment therefore documented a dermal vascular proliferation with the atypical endothelial features described in the case. Kaposi sarcoma, spindle cell hemangioma and angiosarcoma were considered among the differential diagnoses. The case was reported as reactive angioendotheliomatosis with atypical features, and the endothelial atypia was interpreted as treatment-related rather than malignant. The diagnostic challenge centred on the atypical appearance of the vascular proliferation in a patient receiving anticancer treatment. Histopathological findings and the immunohistochemical staining pattern were presented alongside the clinical findings, with strong endothelial marker expression and low Ki-67 positivity characterizing the investigated lesions (**Table 1**).

The cutaneous lesions were managed conservatively with an emollient, topical antibiotics, oral antihistamines and an oral analgesic. Management therefore included topical applications together with oral medication. The local treatment consisted of the emollient and topical antibiotics, whereas the oral component comprised antihistamines and an analgesic. This conservative regimen was used for the tender plaques and ulcerative lesions involving the palms and soles. At presentation, the lesions included

sfirm, non-blanching erythematous plaques, with some having developed a purulent, exudative ulcer base. The treatment described for this cutaneous presentation combined local skin care with oral symptomatic medication. It was provided in the clinical setting of colonic adenocarcinoma treated with FOLFOX and nivolumab, following the presentation of the vascular skin lesions. The dermatological management was described as conservative, encompassing both topical and oral preparations.

Subsequent assessment of the lesions was undertaken at the two-week follow-up, when the clinical response to treatment was reviewed. At the two-week follow-up, the cutaneous lesions had significantly improved following conservative treatment with an emollient, topical antibiotics, oral antihistamines and an oral analgesic. Follow-up photographs showed resolving lesions on the palms and soles, which had initially presented as tender, erythematous plaques and well-defined ulcers with a purulent, exudative base (**Figure 4**).



Figure 1. Initial clinical findings: palmar erythematous plaques with yellow crusting (left) and plantar ulcerative lesions (right).

Table 1. Immunohistochemical findings

Marker	Reported finding
CD31	Strong positivity in arborizing vascular channels
Ki-67	Low positivity

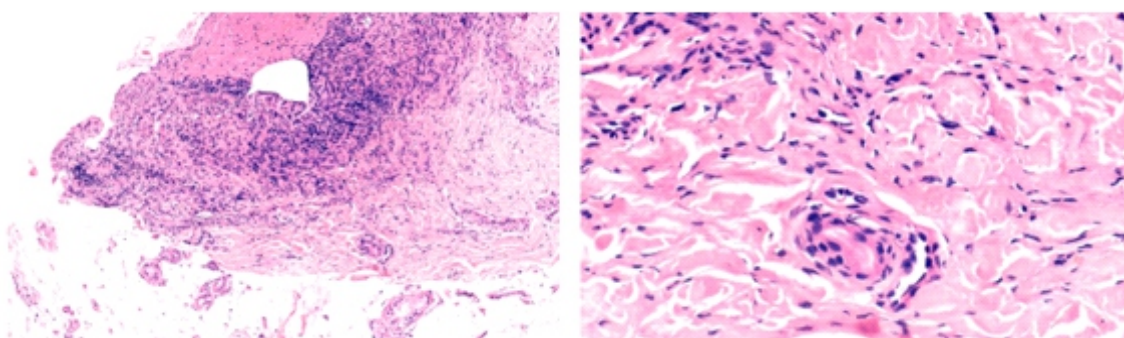


Figure 2. Histopathology demonstrating dermal proliferation of thin blood vessels with plump nuclei.

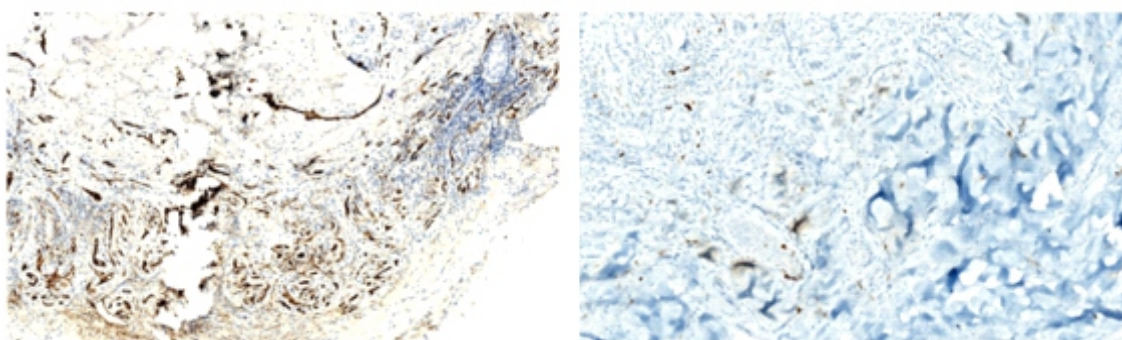


Figure 3. Immunohistochemistry showing CD31 positivity (left) and low Ki-67 positivity (right).



Figure 4. Follow-up photographs showing resolving palmar (left) and plantar (right) lesions after treatment.

DISCUSSION

The present case illustrates the diagnostic complexity of reactive angioendotheliomatosis (RAE) presenting as painful palmo-plantar plaques and ulcers in a woman receiving FOLFOX and nivolumab. McMenamin et al. described heterogeneous clinical and histological patterns in 15 patients, including ulcerated lesions and dermal capillary proliferation, supporting the morphological interpretation in this patient [7]. Kravvas et al. reported painful ulcerative RAE initially resembling pyoderma gangrenosum with cellulitis. Their findings emphasised the importance of biopsy in atypical ulceration. Similarly, the present patient's tender, exudative lesions required histopathological assessment because their clinical appearance alone could not reliably distinguish reactive vascular proliferation from inflammatory or neoplastic disease [4]. Afioni et al. described RAE associated with ulcerative colitis, illustrating its occurrence alongside systemic inflammation. In the present case, malignancy and concurrent anticancer therapies complicated attribution. Although lesions appeared approximately three weeks after nivolumab administration, this temporal association suggested a possible treatment relationship without establishing a definite drug-induced mechanism [2]. Sibaud described diverse immune-mediated cutaneous reactions following checkpoint inhibition. This provided context for considering nivolumab-associated skin toxicity, although it did not specifically establish RAE as a recognised reaction. The unusual vascular histology therefore required independent clinicopathological interpretation rather than attribution to immunotherapy solely because of the timing of onset [8]. Belum et al. identified rash, pruritus and vitiligo as prominent dermatological adverse events associated with PD-1 inhibitors. The ulcerative palmo-plantar vascular lesions in this patient differed from these commonly reported patterns, demonstrating why an atypical eruption during nivolumab therapy warrants tissue examination instead of being classified as nonspecific drug-related dermatitis [9]. Straka et al. reported RAE mimicking Kaposi sarcoma, highlighting diagnostic overlap between reactive and neoplastic vascular lesions. Here, plump endothelial nuclei and focally indistinct lumina raised similar concerns. Strong CD31 expression supported endothelial

differentiation, while low Ki-67 positivity favoured limited proliferative activity; neither finding independently established benignity or excluded malignancy [10]. Douvali et al. described metastatic angiosarcoma initially resembling RAE, underscoring the importance of reassessment when clinical progression contradicts the initial diagnosis. In contrast, this patient's substantial improvement after two weeks of conservative management supported a reactive process. Nevertheless, short-term improvement did not eliminate the value of subsequent clinical surveillance [11]. Coleman et al. reported that many checkpoint inhibitor-associated inflammatory eruptions responded to dermatological treatment. Although their findings were not specific to RAE, this patient's improvement with emollients, topical antibiotics, antihistamines and analgesia supported conservative care in this episode. Overall, the case emphasised careful morphological assessment, cautious causal attribution and continued clinical follow-up [12].

CONCLUSION

This case highlights the diagnostic challenge of reactive angioendotheliomatosis with atypical features arising following nivolumab therapy. The palmo-plantar plaques and ulcers, together with atypical endothelial morphology, required careful clinicopathological correlation to distinguish a reactive vascular proliferation from malignant mimics. Strong CD31 expression and low Ki-67 positivity supported interpretation alongside the clinical and histopathological findings. Significant improvement following two weeks of conservative treatment favoured a reactive process. However, the temporal association with nivolumab did not establish causality, particularly with concurrent chemotherapy and underlying malignancy. Continued clinical follow-up remains important to assess lesion evolution and reconsider the diagnosis if concerning changes develop.

LIMITATIONS & FUTURE PERSPECTIVES

The study's limitations include a single-centre setting, a relatively small sample size, and a short study duration, which may limit the broader applicability of the results. Future studies should incorporate multi-centre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical health-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient care, diagnosis, and treatment outcomes. By highlighting real world relevance, the study contributes to evidence based medical practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

CD31: Cluster of Differentiation 31

FOLFOX: Folinic acid, Fluorouracil, and Oxaliplatin

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

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DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

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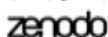
AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research directions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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