# Palpable purpuric eruption mimicking vasculitis following avapritinib

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## INTRODUCTION

Tyrosine kinase (TK) inhibitors (TKI) are a widely used and important class of oncologic agents with diverse and well-described cutaneous adverse events (CAE).[1] Avapritinib is a newly approved selective TKI with activity against tyrosine-protein kinase KIT/CD117 (KIT) and platelet-derived growth factor receptors (PDGFR)used in the treatment of gastrointestinal stromal tumors (GIST) harboring specific exon 18 mutations.[2] Here we present a case of an avapritinib-induced palpable purpuric eruption clinically mimicking cutaneous leukocytoclastic vasculitis (LCV).

*Abbreviations used:*

| | |
|---|---|
| CAE: | cutaneous adverse events |
| GIST: | gastrointestinal stromal tumor |
| KIT: | tyrosine-protein kinase KIT/CD117 |
| LCV: | leukocytoclastic vasculitis |
| PDGFRA: | platelet-derived growth factor receptor alpha |
| TK: | tyrosine kinase |
| TKI: | tyrosine kinase inhibitor |

## CASE REPORT

A 68-year-old man on treatment for GIST presented to the clinic after developing a rapidly progressive and pruritic eruption lasting for 3 days. Twelve days prior to presentation, the patient was switched from imatinib to avapritinib 300 mg daily after molecular testing revealed a platelet-derived growth factor receptor alfa (PDGFRA) exon 18 mutation. The patient had no history of recent illness or other medication changes, and review of symptoms was negative. His rash began as pruritic red macules on his arms and quickly developed into purpuric papules, which spread to his back, chest, lower legs, and buttocks.

On presentation, the patient was afebrile and well-appearing. Physical examination revealed numerous 5-10 mm deep, red-to-violaceous, nonblanching, purpuric papules coalescing into plaques symmetrically involving the distal extremities and with spotty involvement of the chest and back (Fig 1, *A*). Several lesions featured superficial vesiculation and perilesional pallor (Fig 1, *B*). On the hard palate, there were a few pinpoint petechiae without erosions (Fig 1, *C*). Punch biopsies of the left arm from 3-day old lesions were performed for hematoxylin-eosin staining and direct immunofluorescence (perilesional) microscopy, and a urinalysis was obtained for a presumed diagnosed of avapritinib-induced LCV. Lab evaluation showed a normal complete blood cell count, normal basic metabolic panel, and normal platelet count of 146,000/$\mu$L (normal, 140.000-390.000/$\mu$L). Urinalysis was normal. The patient was not taking any antiplatelet or anticoagulation medications and denied over-the-counter medication use. Avapritinib was discontinued, and the patient was started on a 15-day oral prednisone taper, beginning at 1 mg/kg daily, in addition to topical clobetasol 0.1% ointment twice daily.

At 1-week follow-up, the patient's rash had markedly improved with resolution of pruritus and flattening and fading of existing lesions. Direct immunofluorescence microscopy was negative for

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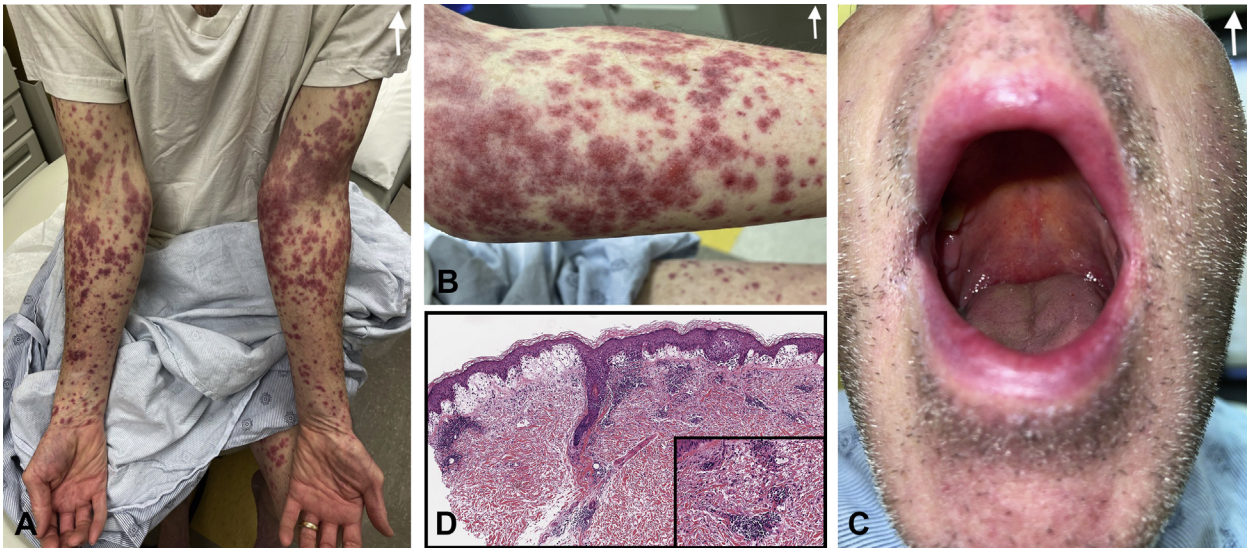


**Fig 1.** Avapritinib-induced drug eruption. **A,** Deep red-to-violaceous nonblanching purpuric papules coalescing into plaques symmetrically involving the distal extremities. **B,** Close-up view of left arm demonstrating superficial vesiculation and perilesional pallor. **C,** Pinpoint petechiae without erosions on the palate. **D,** Punch biopsy revealing perivascular lymphocytic dermatitis with eosinophils and papillary dermal edema without evidence of vasculitis (**A** and **B,** Hematoxylin-eosin stain; original magnifications: **A,** 40×; **B,** 100×).

immune deposits, and hematoxylin-eosin staining revealed a perivascular lymphocytic dermatitis with eosinophils and papillary dermal edema without evidence of vasculitis (Fig 1, *D*) most suggestive of an urticarial hypersensitivity reaction. The prednisone taper was continued, and the patient restarted avapritinib at a reduced dose of 100 mg every other day. At the 2-week follow-up, his rash had completely resolved, and he continues to tolerate his reduced dose.

## DISCUSSION

Receptor tyrosine kinases are important regulatory signaling proteins that play a central role in cancer growth, survival, and metastasis.[3] Targeted TKIs have been increasingly developed and employed in cancer therapy.[3] Diverse CAE have been described with TKI use, including morbilliform drug reactions, psoriasis, papulopustular eruptions, lichenoid reactions, urticaria, LCV, and Stevens-Johnson syndrome, among others.[1,4]

GIST are soft tissue sarcomas arising in the gastrointestinal tract. The majority of GIST harbor activating mutations in PDGFRA and KIT, both of which are receptor TKs.[2] Several TKIs that target PDGFRA and KIT have been developed, including imatinib, sunitinib, and regorafenib (first, second, and third-line therapies for GIST, respectively).[2] However, due to the attainment of secondary mutations in KIT, most patients with GIST develop resistance to these agents.[2] Up to 6% of metastatic or unresectable GISTs develop the specific PDGFRA D842V mutation, which confers pan-resistance to the aforementioned treatments.[2] Hence, this incited the development of avapritinib, a PDGFRA/KIT TKI, which was recently approved in the United States for patients with metastatic or unresectable GIST with PDGFRA exon 18 mutations, including PDGFRA D842V mutations.[2]

Similar to the wide range of skin changes observed broadly with TKI use, CAE from TKIs targeting KIT and PDGFRA receptors are varied and include skin discoloration, morbilliform and lichenoid eruptions, psoriasiform dermatitis, Stevens-Johnson syndrome, urticaria, acute generalized exanthematous pustulosis, hand-foot syndrome, and cheilitis.[1,5,6] C-Kit is normally expressed on melanocytes, epithelial cells of the breast, dermal sweat glands, and tissue mast cells, whereas keratinocytes are abundant in PDGFRA receptors.[1] Thus, blockage of these receptors is likely a direct pathologic factor in the development of cutaneous reaction.[1] Table I summarizes all prior observed CAE attributed to avapritinib.[7-11]

Because avapritinib is a PDGFRA inhibitor, we speculate that inhibition of PDGFR can play a role in vascular leakage, leading to dramatic papillary dermal edema and eventual purpura. PDGF plays a role in vessel maturation by signaling TK receptors and recruiting pericytes to endothelial cells.[12]

**Table I.** Summary of cutaneous adverse effects of avapritinib in the literature

| Dose | Diagnosis of PDGFRA/ KIT+ GIST | Response | Progression-free time | Outcomes | Cutaneous toxicity | Reference |
|---|---|---|---|---|---|---|
| 300 mg | Yes | SD for 2 months | 2 months | Restarted avapritinib at 100 mg | Grade 2-3 palpable purpuric eruption | This case report |
| 300 mg | No | Initial PR at 2 months followed by PD at 11 months | 11 months | Death | Grade 2 cutaneous vasculitis | Cocorocchio et al[7] |
| 300 mg | Yes | Initial SD at 3 months followed by PD at 6 months | 6 months | On ripretinib | Grade 3 rash* | Verma et al[8] |
| 300 mg | Yes | Initial PR at 2 months, SD at 5 months followed by PD at 8 months | 8 months | Plan for ripretinib | Grade 2 rash | Verma et al[8] |
| 300 mg | Yes | PD | 5 months | Plan for ripretinib | Grade 2 rash | Verma et al[8] |
| <300 mg (n = 4) | Yes | X | X | X | Grade 1-2 rash | Heinrich et al[9] |
| 300 mg (n = 1) | Yes | X | X | X | Grade 1-2 rash | Heinrich et al[9] |
| 400 mg (n = 2) | Yes | X | X | X | Grade 1-2 rash | Heinrich et al[9] |
| 600 mg (n = 1) | Yes | X | X | X | Grade 2 dermatitis acneiform | Heinrich et al[9] |
| 300-400 mg (n = 21) | Yes | X | X | X | 20 with grade 1-2 rash, 1 with grade ≥ 3 rash | George et al[10] |
| 300 mg (n = 19) | Yes | X | X | X | 18 with grade 1-2 rash, 1 with grade ≥ 3 rash | Joseph et al[11] |
| 400 mg (n = 10) | Yes | X | X | X | 10 with grade 1-2 rash | Joseph et al[11] |

Of note, ''rash'' in many of these studies was nonspecific or lacked any specifiers in general.
*GIST,* Rastrointestinal stromal tumors; *KIT,* tyrosine-protein kinase KIT/CD117; *PD,* progressive disease; *PDGFRA,* platelet-derived growth factor receptor alpha; *PR,* partial response; *SD*, stable disease; *X,* not reported.
*'Rash' includes rash, rash erythematous, rash macular, rash generalized, and rash papular.

Pericytes are vascular mural cells that are in the vascular basement membrane of capillaries, arterioles, and venules and that are in contact with the endothelium.[13] Studies have shown that disruption of PDGF and PDGFR genes results in the formation of blood vessels that lack pericytes, which suggests that PDGF and PDGFR are involved in the recruitment of pericytes.[12] Pericytes play an important role in mediating physiologic and pathologic repair processes; they promote vessel formation, vessel contraction and dilatation, and endothelial barrier function.[12,13] The lack of recruitment of pericytes can result in an increased capillary diameter, increased endothelial permeability, and abnormal distribution of junctional proteins.[12] While this speaks to the role of PDGF in vessel maturation, we postulate that inhibition of PDGF may affect the function of pericytes and can lead to vascular leakage and a disrupted junctional structure, resulting in purpura.

Our patient presented with a palpable, pruritic eruption that favored the extremities one week after starting avapritinib, making the patient's drug history and physical examination suggestive of avapritinib-induced LCV. Notably, however, this patient's pathology findings were more suggestive of an urticarial drug eruption, with pathology showing perivascular lymphocytic dermatitis with scattered eosinophils and papillary dermal edema.

To our knowledge, this is the first avapritinib-induced eruption with histopathologic analysis and the first described case of a patient who was able to tolerate resumption of avapritinib after systemic corticosteroid treatment. Of note, there was a case of grade 2 cutaneous vasculitis in a patient with mucosal metastatic melanoma who was treated with avapritinib, but no biopsy results were reported to confirm vasculitis.[7] It is interesting to note that a similar eruption characterized as palpable, nonblanching, violaceous, pruritic papules and plaques mimicking LCV has been described secondary to the use of ibrutinib, which is a Bruton TKI.[14] In these patients, histopathologic analysis revealed perivascular infiltration of lymphocytes, neutrophils, and eosinophils involving the papillary dermis, and no signs of vasculitis.[14] Clinicians prescribing avapritinib should be aware of this palpable, purpuric eruption that can mimic LCV and consider evaluation with histopathology to better guide treatment.

**Conflicts of interest**

None disclosed.

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