Multiple New-Onset Pyogenic Granulomas During Treatment With Paclitaxel and Ramucirumab

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PRACTICE **POINTS**

- Pyogenic granulomas (PGs) are benign vascular tumors that clinically are characterized as small, eruptive, friable papules.
- Ramucirumab is a monoclonal antibody against vascular endothelial growth factor receptor 2.
- Some patients experience paradoxical formation of vascular tumors such as PGs when treated with combination therapy with ramucirumab and a taxane such as paclitaxel.

To the Editor:

Pyogenic granuloma (PG) is a benign vascular tumor that clinically is characterized as a small eruptive friable papule.[1] Lesions typically are solitary and most commonly occur in children but also are associated with pregnancy; trauma to the skin or mucosa; and use of certain medications such as isotretinoin, capecitabine, vemurafenib, or indinavir.[1] Numerous antineoplastic medications have been associated with the development of solitary PGs, including the taxane mitotic inhibitor paclitaxel (PTX) and the vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody ramucirumab.[2] We report a case of multiple PGs in a patient undergoing treatment with PTX and ramucirumab.

A 59-year-old woman presented to the dermatology clinic with red, itchy, bleeding skin lesions on the breast, superior chest, left cheek, and forearm of 1 month's duration. She denied any preceding trauma to the areas. Her medical history was notable for gastroesophageal junction adenocarcinoma diagnosed more than 2 years prior to presentation. Her original treatment regimen included nivolumab, which was discontinued for unknown reasons 5 months prior to presentation, and she was started on combination therapy with PTX and ramucirumab at that time. She noted the formation of small red papules 2 months after the initiation of PTX-ramucirumab combination therapy, which grew larger over the course of the next month. Physical examination revealed 5 friable hemorrhagic papules and nodules ranging in size from 3 to 10 mm on the chest, cheek, and forearm consistent with PGs (Figure 1). Several scattered cherry angiomas were noted on the scalp and torso, but the patient reported these were not new. Biopsies of the PGs demonstrated

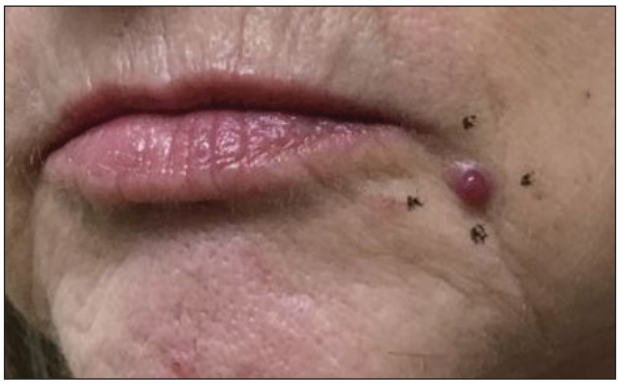

FIGURE 1. New-onset pyogenic granuloma on the left cheek following combination therapy with paclitaxel and ramucirumab.

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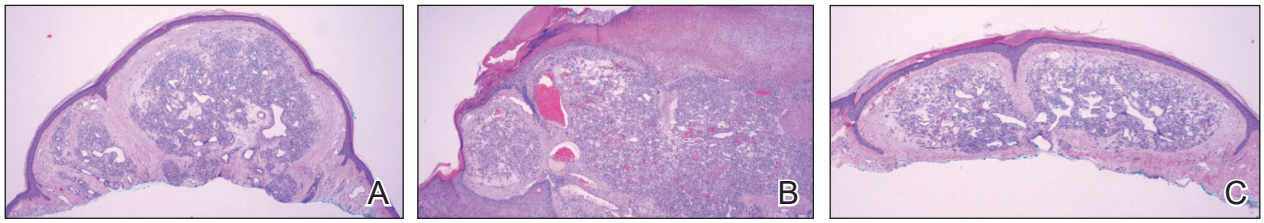

FIGURE 2. A–C, Histopathology from the left cheek, medial breast, and medial superior chest demonstrated lobular aggregates of small-caliber vessels set in an edematous inflamed stroma and partially enclosed by small collarettes of adnexal epithelium, consistent with pyogenic granuloma (H&E; original magnifications ×40, ×100, and ×40, respectively).

Pyogenic Granulomas in Patients Undergoing Treatment With Paclitaxel and Ramucirumab

Reference (year)	Gender	Age, y	Drug	No. of lesions	Lesion location	Size, mm	Months to lesion from therapy initiation	Type of cancer
Paul and Cohen[3] (2012)	F	68	P	1	Subungual	U	3	Breast
Alessandrini et al[4] (2019)	U	U	P	1	Subungual	U	U	U
Watanabe et al[5] (2019)	M	76	P, R	1	Cheek	7	2	Gastric
	M	70	P, R	1	Cheek	10	3	
	M	69	P, R	1	Occipital scalp	10	2	
	M	75	P, R	1	Lower lip	10	6[a]	
Ibe et al[6] (2019)	F	48	R[b]	1	Thumb joint	20	1	Lung
Choi et al[7] (2020)	M	40	P, R	1	Parietal scalp	8	4	Gastric
Aragaki et al[8] (2021)	M	55	P, R	1	Tongue	6	7	Gastric
	M	67	P, R	1	Upper mucosal lip	5	5	
Current report	F	59	P, R	5	Breast	10	4	Gastroesophageal
					Superior chest	4		
					Superior chest	3		
					Left cheek	4		
					Forearm	5		

Abbreviations: F, female; M, male; P, paclitaxel; R, ramucirumab; U, unknown.

[a]Treatment began 6 months prior, including a 3-month withdrawal period; lesion appeared 2 weeks after treatment was restarted.

[b]Patient was on treatment with ramucirumab and docetaxel.

lobular aggregates of small-caliber vessels set in an edematous inflamed stroma and partially enclosed by small collarettes of adnexal epithelium, confirming the clinical diagnosis of multiple PGs (Figure 2).

The first case of PTX-associated PG was reported in 2012.[3] Based on a PubMed search of articles indexed for MEDLINE using the terms *pyogenic granuloma*, *lobular capillary hemangioma*, *paclitaxel*, *taxane*, and *ramucirumab,* there have been 9 cases of solitary PG development in the setting of PTX alone or in combination with ramucirumab since 2019 (Table).[3-8] Pyogenic granulomas reported in patients who were treated exclusively with PTX were subungual, while the cases resulting from combined therapy were present on the scalp, face, oral mucosa, and surfaces of the hands sparing the nails. Ibe et al[6] reported PG in a patient who received ramucirumab therapy without PTX but in combination with another taxane, docetaxel, which itself has been reported to cause subungual PG when used alone.[9] Our case of the simultaneous development of multiple PGs in the setting of combined PTX and ramucirumab therapy added to the cutaneous distributions for which therapy-induced PGs have been observed (Table).

The development of PG, a vascular tumor, during treatment with the VEGFR2 inhibitor ramucirumab—whose mechanism of action is to inhibit angioneogenesis—is inherently paradoxical. In 2015, a rapidly expanding angioma with a mutation in the kinase domain receptor gene, *KDR*, that encodes VEGFR2 was identified in a patient undergoing ramucirumab therapy. The authors suggested that *KDR* mutation resulted in paradoxical activation of VEGFR2 in the setting of ramucirumab therapy.[10] Since then, ramucirumab and PTX were suggested to have a synergistic effect in vascular proliferation,[5] though an exact mechanism has not been proposed. Other authors have identified increased expression of VEGFR2 in biopsy specimens of PG during combined ramucirumab and taxane therapy.[6] Although genetic studies have not been used to evaluate for the presence of *KDR* mutations specifically in our patient population, it is possible that patients who develop PG and other vascular tumors during combined taxane and ramucirumab therapy have a mutation that makes them more susceptible to VEGFR2 upregulation. UV exposure may have a role in the formation of PG in patients on combined ramucirumab and taxane therapy[7]; however, our patient's lesions were distributed on both sun-exposed and unexposed areas. Although potential clinical implications have not yet been thoroughly investigated, following long-term outcomes for these patients may provide important information on the efficacy of the antineoplastic regimen in the subset of patients who develop cutaneous vascular tumors during antiangiogenic treatment.

Combination therapy with PTX and ramucirumab has been associated with the paradoxical development of cutaneous vascular tumors. We report a case of multiple new-onset PGs in a patient undergoing this treatment regimen.

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