Angiokeratoma-like purpuric palmar nodules following chemotherapy

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Abstract

We describe a patient with leukemia undergoing chemotherapy who developed painful purpuric nodules of the digits. These findings were concerning for endocarditis (clinically) and angiokeratomas on gross histology. After extensive evaluation, we report the development of painful purpuric nodules as a likely side effect of the patient's therapeutic regimen (hydroxyurea, daunorubicin, cytarabine, and methotrexate).

Keywords: angiokeratoma, chemotherapy, cutaneous chemotherapy side effect, cytarabine, daunorubicin, intraepithelial hemorrhage, microemboli, Osler nodes, painful purpuric nodules

Introduction

Chemotherapy commonly causes changes in the hair, skin, nails, and mucous membranes. From classic, non-targeted chemotherapeutics to novel, bioengineered treatments, cutaneous side effects vary widely. Although some skin manifestations are well-studied and readily recognized, others are rare and newly described [1]. We herein report a challenging case of purpuric cutaneous nodules, developing in the setting of leukemia and induction chemotherapy that clinically mimicked septic microemboli. However, on gross histology these lesions resembled angiokeratomas and may represent a previously uncharacterized side effect of chemotherapy.

Case Synopsis

A 47-year-old woman with a remote history of breast cancer and a new diagnosis of mixed lineage acute leukemia was admitted to the hospital for induction chemotherapy. Initial white blood cell (WBC) count revealed 271.2×10^3 leukocytes/μL (normal range: $4.5–11\times10^3$ leukocytes/μL) with 85% blasts. On day one after admission, she received hydroxyurea and on day three she began a "7+3" induction regimen of daunorubicin and cytarabine resulting in severe leukopenia (WBC 0.3×10^3 leukocytes/μL). Clinical course is detailed in **Figure 1**. She concluded the aforementioned chemotherapeutic regimen on day 9 of admission. On day two of her hospital course, the patient developed a neutropenic fever with an unrevealing urinalysis, chest radiograph, and blood cultures; she was subsequently started on cefepime, acyclovir, and posaconazole.

She continued to experience episodic fevers for the subsequent two weeks, again with unrevealing urinalysis, chest radiograph, and blood cultures. On day 23 of her hospital course, the patient reported palmar desquamation followed by the development of painful, violaceous nodules on the fingers (**Figure 2**). The patient received an additional dose of cytarabine (day 13) and a single dose of methotrexate (day 17). Other medications received

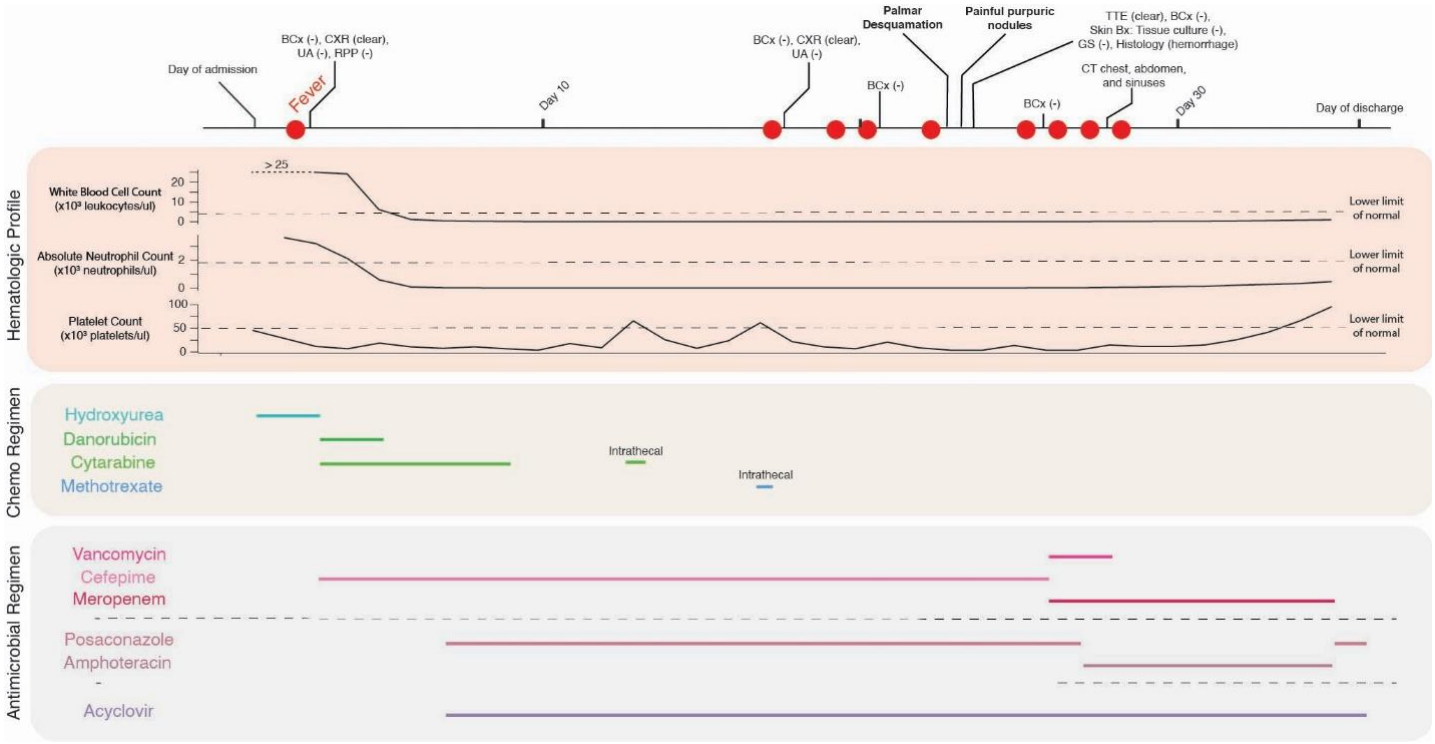

Figure 1. *Clinical course highlighting the relationship between cutaneous findings and the chemotherapeutic regimen, fevers, hematologic profile, infectious workup, and antimicrobial regimen.*

around the time of lesion appearance included chlorhexidine gluconate, diphenhydramine, magnesium and potassium supplements, melatonin, a multivitamin, oxycodone, acetaminophen, and benzonatate capsules. The patient did not receive fingerstick glucose monitoring prior to lesion development.

Physical examination was notable for multiple, discrete, dark purpuric papules and nodules present on the distal volar digits (**Figure 2**). Accompanying palmar erythema and desquamating hyperkeratosis of the hands was noted. Acrylic nails were in place, but the cuticles did not show splinter hemorrhage. Petechiae were observed on the conjunctiva and the posterior pharynx. She remained pancytopenic with platelets of 4×10^3/µL (normal range: 150-450×10^3 platelets/µL).

Figure 2. *Purpuric papules and nodules on the volar hands with widespread palmar desquamation.*

The patient noted similar palmar erythema and acral peeling years prior, after undergoing chemotherapy for breast cancer. She had never previously experienced the tender nodules. Given her immunosuppression, recurrent fevers, and new cutaneous lesions concerning for septic microemboli (Osler nodes), punch biopsy of a cutaneous lesion for hematoxylin & eosin and tissue culture were completed. The patient's antimicrobial regimen was broadened to vancomycin, meropenem, and amphotericin; work-up for infective endocarditis ensued. Transthoracic echocardiogram showed no evidence of vegetations or new valvular disease and repeat blood cultures grew no organisms. The punch biopsy showed epidermal acanthosis with elongation of the rete ridges. Intraepithelial collections of erythrocytes were initially believed to

represent well-formed vascular channels (**Figure 3A**, inset). However, surrounding endothelial cells were not easily identified on close examination of H&E-stained sections and were further not identified with immunohistochemical staining for CD31 (**Figure 3B**). Papillary dermal vascular ectasia and scant dermal hemorrhage were also noted (**Figure 3A**). A Gram stain failed to identify bacterial microorganisms in the tissue. Tissue cultures (bacterial, acid-fast bacilli, and fungal) also proved unrevealing. Over the subsequent week, the patient's fever subsided and her antimicrobial regimen was narrowed to prophylactic acyclovir and posaconazole. Approximately three to four weeks after the last dose of systemic chemotherapy, the original purpuric papules began to resolve and no new skin lesions emerged. The patient's hematologic profile began to recover and she was discharged in good health.

Case Discussion

An infectious etiology may be elucidated in up to 30% of patients with neutropenic fever [2]. Cutaneous lesions may offer an early clue to diagnosis and guide the selection of specific testing [2]. The appearance of painful, purpuric nodules, reminiscent of Osler "ephemeral spots of painful nodular erythema," are classic stigmata of infective endocarditis [3]. However, Osler nodes are a rare finding (~3% of cases), [4]. The clinical diagnosis of infective endocarditis relies primarily on the growth of microorganisms in blood culture and echocardiographic evidence of endocardial involvement (in addition to other, less sensitive manifestations described in the DUKE criteria), [5]. In our patient, multiple blood cultures were without growth and a transthoracic echocardiogram showed no evidence of infection. Skin biopsy failed to exhibit septic microemboli responsible for Osler nodes [6].

Thrombocytopenic purpura are a well-documented manifestation of chemotherapy; erythrocyte extravasation limited to the dermis and hypodermis are typically present on histopathology [7]. Our case exhibited epidermal hyperplasia and significant intraepidermal hemorrhage (**Figure 3**). Intraepidermal vascular endothelial cells, as can often be seen in angiokeratomas when vascular channels herniate into the epidermis, could not be readily identified on H&E.

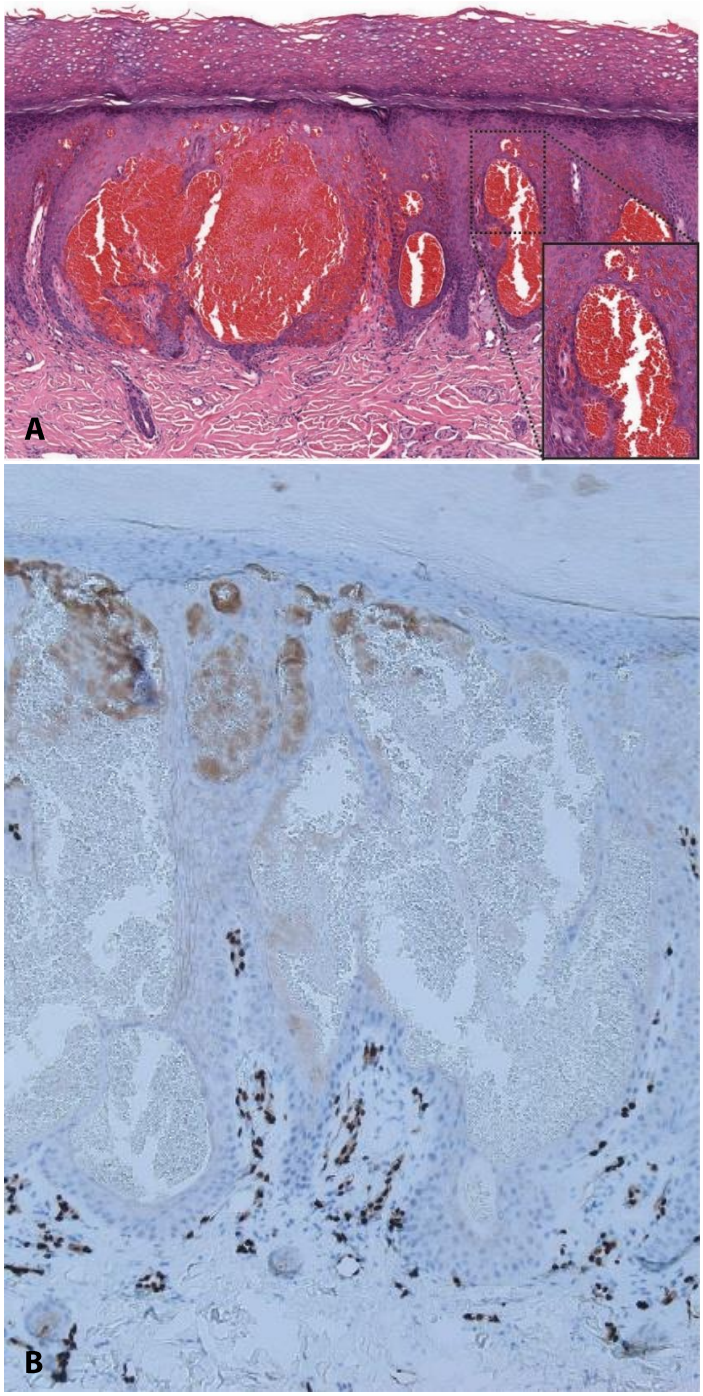

Figure 3. ***A)*** *Punch biopsy showing epidermal hyperplasia with intraepidermal vascular collections and papillary dermal vascular ectasia suggestive of angiokeratoma. H&E, 5×. Inset bottom right corner shows the majority of hemorrhage is intraepidermal, H&E, 20×.* ***B)*** *CD31 immunohistochemical staining reveals that the hemorrhage is not surrounded by endothelial cells.*

Angiokeratomas develop from a dilation of blood vessels in the superficial papillary dermis, followed by secondary hyperkeratosis [8]. The initial trigger for vascular ectasia may differ depending on the type of angiokeratoma and in many cases, remains unknown. When widespread, a genetic mutation may be causative (such as in Fabry disease), [8]. In localized lesions, chronic trauma is often cited [8]. We considered whether blood glucose monitoring finger sticks could be a source of trauma but the patient was not receiving monitoring immediately preceding the eruption and many of the nodules appeared on the proximal aspect of the digits (where finger sticks would not take place). We also considered whether the desquamating rash (likely secondary to chemotoxicity) could have induced microtrauma leading to hemorrhagic lesions. However, many of the purpuric nodules were present on regions free of desquamation. At least 5 cases describe the development of angiokeratoma-like lesions following initiation of medications (**Table 1**), such as enoxaparin and etanercept [9–11]. Although never reported as a side effect of chemotherapy, it is possible that our patient's lesions developed as a reaction to her treatment. In the aforementioned drug-induced cases, the emergence and resolution of the lesions was temporally related to medication initiation, whereby the lesions appeared within weeks of medication use (with the exception of one case in which lesions appeared after 14 months) and resolved weeks after the initial evaluation [9]. Similarly, our patient's lesions appeared two to three weeks after her first dose of chemotherapy and began to resolve three to four weeks after the regimen was stopped, lasting a total of 5 to 7 weeks. Importantly, although appearing angiokeratoma-like on H&E, our patient's nodules could be distinguished by negative CD31 staining in the epidermis. Our patient received multiple medications (hydroxyurea, daunorubicin, cytarabine, methotrexate, and several antimicrobials), making it difficult to pinpoint a single, causative agent.

Conclusion

We herein report the novel development of angiokeratoma-like lesions following chemotherapy. This may represent a rare side effect of chemotherapy and awareness of its existence can help guide diagnosis and clinical management. This case highlights the diagnostic challenge of rare chemotoxicities, particularly in immunosuppressed patients. We report the development of painful purpuric nodules resemblant of angiokeratomas as novel reaction to chemotherapy.

Potential conflicts of interest

Dr. Rosenbach reports grants and personal fees from Processa, and personal fees from Merck, Janssen, aTyr, and AMA/JAMA, outside the submitted work. All other authors in this manuscript have no conflicts of interest to report.

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Table 1. *Case reports of angiokeratoma-like lesions following initiation of medications.*

Age	Sex	Main medical Problem/ Reason for admission	Potential causative agent	Location of lesion	Time from drug initiation to onset of lesions	Treatment	Total duration of lesions	Ref
47	Female	Leukemia	Chemotherapeutics: hydroxyurea, daunorubicin, cytarabine, and methotrexate. Antimicrobials: cefepime, posaconazole, acyclovir	Palms	2-3 weeks	None	5 -7 weeks	This case report
61	Female	Pulmonary Embolism	Enoxaparin	Abdomen, right arm, left breast, and left fifth toe	1-2 weeks	Lowered Enoxaparin dose	Initial lesions resolved but new lesions appeared occasionally	[9]
43	Male	Psoriasis and Psoriatic Arthritis	Etanercept	Injection sites (abdomen and thigh)	14 months of ongoing treatment, but lesions appeared within 2 weeks of a relapse	Not described	Not described	[10]
72	Female	CNS Lymphoma	Enoxaparin	Lower and upper extremities, and abdomen	~2 weeks	None	4 weeks	[10]
52	Female	Evaluation for heart transplant	Unfractionated Heparin	Face, shoulders, lower abdomen, back, and left dorsal aspect of the hand	~4 months	None	~5 months	[10]
45	Male	Valvular heart disease	Heparin	Hands and legs	several weeks (no further detail provided in the report)	None	several weeks (no further detail provided in the report)	[10]