Cutaneous granulocytic sarcoma and Koebner phenomenon in a context of myelodysplastic syndrome

Constance Nizery-Guermeur, MD,a Christelle Le Gall-Ianotto, PhD,a,b Emilie Brenaut, MD,a,b Marie-Anne Couturier, MD, c Matthieu Talagas, MD, b,d Sophie Andrieu-Key, MD, d Gaelle Guillerm, MD,c Laurent Misery, PhD, MD,a,b and Allan Karam, MD b

Brest, France

Key words: granulocytic sarcoma; Koebner phenomenon; myelodysplastic syndrome; transforming growth factor—beta 1 pathway.

INTRODUCTION

Granulocytic sarcoma (GS) is also known as myeloid sarcoma or chloroma because of its green hue caused by myeloperoxidase (MPO). This disease involves the localization of myeloblasts or immature myeloid cells to an extramedullary site. GS has been described at numerous anatomic sites, but cutaneous GS (CGS) is uncommon. Although CGS is rare, it is clearly associated with myeloid disorders, such as acute myeloid leukemia, myeloproliferative neoplasms, and myelodysplastic syndromes (MDSs). CGS may herald acute transformation, and it is associated with a poor prognosis.1-3 However, the mechanism underlying the specific migration of myeloblasts to the skin remains uncertain. In 2008, Kawakami et al4 presumed that transforming growth factor (TGF-β1) released by hematopoietic cells within the cutaneous extramedullary hematopoiesis could play a role in the onset of such skin lesions.4

We report a case of a patient with MDS presenting with 2 CGSs that developed consecutively at traumatized skin sites, suggestive of the Koebner phenomenon (KP). Immunohistochemical (IHC) analysis confirmed the expression of TGF-β1 on myeloblasts and fibroblasts that had infiltrated the CGSs but also showed the expression of its specific receptor (TGF-β1R), suggesting a role for this cytokine in cutaneous tropism and the pathogenesis of the KP.

From the Department of Dermatology, University Hospital of Brest; Laboratory of Neurosciences of Brest (EA4685), University of Western Brittany; Department of Clinical Hematology, University Hospital of Brest; and Laboratory of Pathology, University Hospital of Brest. Drs Nizery-Guermeur and Gall-Ianotto contributed equally to this work. Funding sources: None. Conflicts of interest: None declared.

CASE REPORT

A 77-year-old man was admitted to our dermatology department with fevers and a 1-month history of a hematoma on the left thigh, evolving in an indurated necrotizing ulcerative plaque (Fig 1). MDS was diagnosed 18 months prior (refractory anemia with excess blasts I, normal molecular cytogenetics, trisomy 8 in the tumoral clone), which was treated with norethandrolone. A complete blood count on admission showed hemoglobin at 8.2 g/dL (normal ranges, 12.4-14.9 g/dL), platelet level at 28 G/L (normal ranges, 150-400 G/L), a leukocytosis count at 5.8 10³/mm³ (normal ranges, 4-10.10³/mm³) but with circulating blast cells, and a C-reactive protein level of 117 mg/L (normal, <6 mg/mL). Bone marrow analysis confirmed qualitative abnormalities of the

Abbreviations used:

CGS: cutaneous granulocytic sarcoma
GS: granulocytic sarcoma
IHC: immunohistochemistry
KP: Koebner phenomenon
MDS: myelodysplastic syndrome
MPO: myeloperoxidase
PG: pyoderma gangrenosum
TGF-β1: transforming growth factor-beta 1
TGF-β1R: transforming growth factor-beta 1 receptor

Correspondence to: Christelle Le Gall-Ianotto, PhD, Laboratory of Neurosciences of Brest, 22 Avenue Camille Desmoulins, F-29200 Brest. E-mail: christelle_legall@hotmail.com.
JAAD Case Reports 2015;1:207-11.
2352-5126 © 2015 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
http://dx.doi.org/10.1016/j.jdcr.2015.04.012

207
trilineage, with myeloblasts constituting 7% of the nucleated bone marrow cells.

A culture of the lesion found numerous *Staphylococcus aureus* colonies, but no other organisms were identified. Histopathologic examination of skin biopsies found a dense infiltration of blast cells with round, not lobulated nuclei and scant cytoplasm. The phenotype of myeloblasts was characterized by various immunostains (CD45, MPO, MiB1, CD15, CD99, CD15, CD68, CD34, CD99, and CD68) allowing the diagnosis of CGS (Fig 1, B and C). A supplementary IHC analysis found that TGF-β1 and its specific receptor, TGF-β1R, were highly expressed in immature hematopoietic cells and dermal fibroblasts within the GS (Fig 2, A and B). The cutaneous lesion had completely resolved 3 weeks after the resolution of fevers, and the blood count normalized after treatment with antibiotics (cloxacillin for 18 days, 1 g 3 times per day). Skin biopsy results confirmed the complete regression of the GS.

Several days later, complete excision of a squamous cell carcinoma located on the cheek was performed. No myeloblasts were observed by histologic examination of this lesion. However, during the wound healing process (10 days after surgery), a second GS was identified as a purple plaque that had infiltrated and ulcerated around the surgical wound (myeloblasts identified as CD45+, MPO+, MiB1+, and CD34−; Fig 3). Similar to the first GS detected, expression of TGF-β1 and TGF-β1R was observed on myeloblasts and dermal fibroblasts within the GS (Fig 2, C and D). Complete and spontaneous regression of the lesion was observed 3 weeks later.

Eighteen months later, the patient was still alive and had received chemotherapy treatment, which had been initiated after his GS episodes (3 rounds of cytarabine/mitoxantrone) but did not cure his MDS. Cutaneous surgery was avoided, and no skin lesions were observed. No additional GS was diagnosed.

**DISCUSSION**

We describe 2 episodes of CGS that occurred after trauma (hematoma and cutaneous surgery) in the context of MDS. The differential diagnosis included pyoderma gangrenosum (PG) and aleukemic leukemia cutis. PG, the most common
Fig 2. IHC costaining of TGF-β1 and TGF-β1R (in red, white arrows) and MPO in brown in the GS on the left thigh (A and B) and right cheek (C and D). A, TGF-β1 and B, TGF-β1R expression in immature hematopoietic cells and dermal fibroblasts within the cutaneous GS on the left thigh. C, TGF-β1 and D, TGF-β1R expression in immature hematopoietic cells and dermal fibroblasts within the cutaneous GS on the right cheek. (Scale bar = 10 μm.)

Fig 3. A, Lesions on the right cheek that developed after excision of squamous cell carcinoma. B, Hematoxylin-eosin stain of the right cheek biopsy revealed numerous myeloblastic cells within the GS (magnification, ×100; inset, ×400). C, IHC for MPO (1/300) showed the presence of numerous myeloblasts (original magnification, ×400).
neutrophilic dermatosis described in MDS, was excluded based on several clinical and histopathologic characteristics. Clinically, the lesions did not start as papules or pustules, were asymptomatic, and were not associated with constitutional symptoms. Histologically, the infiltrate of cells was dense in the junction between dermis and subcutis and composed of myeloblasts rather than a massive dermal-epidermal neutrophilic infiltrate with suppurative/abscess formation as in PG. Aleukemic leukemia cutis was excluded based on the absence of leukemic evolution 2 years after the skin lesions developed and the negativity of CD34 and CD117 stains on infiltrated blast cells.

This type of GS resulting from skin trauma is termed the KP or isomorphic response. The KP has been associated classically with dermatologic diseases (eg, psoriasis, lichen sclerosus), but it has also been described in association with systemic diseases. Some cases of GS occurring after a trauma have been reported that did not result from the KP, such as a GS that developed in a preexisting hydroxyurea-induced leg ulcer in a polycythemia vera patient and a GS masquerading as a perianal abscess. Furthermore, a “pseudo-Koebner” response was reported in an MDS patient, but the absence of hematopoietic cells in the skin biopsies did not allow for the verification of this case as the true KP. In our case, the hematopoietic cells detected in the skin biopsies during the wound healing process were suggestive of the KP. Similar to GS, the pathogenesis of the KP remains obscure and has not been extensively studied. However, involvement of inflammatory cells and local production of various cytokines and adhesion molecules have been suspected.

The expression of chemokine receptors, cytokines, and adhesion molecules by myeloblasts and various skin cells could explain the localization of GS to the skin. Byrd et al found that the expression of CD56, an adhesion molecule, on blast cells was a risk factor for extramedullary tumors in one MDS case. In our case, IHC analysis of skin samples found overexpression of the TGF-β1/TGF-β1R pathway in immature hematopoietic cells and dermal fibroblasts during cutaneous extramedullary hematopoiesis. Only expression of TGF-β1 in association with MDS was reported in the literature to date. TGF-β1 has long been recognized as a key molecule acting both during wound repair and tumor formation. Indeed, it is a growth factor synthesized by skin cells (eg, keratinocytes, fibroblasts) and actively participates in the skin wound healing process by increasing the inflammatory response, promoting both myofibroblast activation and survival and extracellular matrix remodeling. Thus, it was not surprising to find TGF-β1 in our case, but its expression on myeloblasts within the GS suggested that this cytokine could be involved in the onset of CGS. In MDS, the TGF-β1 pathway is constitutively activated in MDS progenitors, suggesting that these hematopoietic cells are more sensitive to this cytokine. In any event, novel therapeutics targeting the TGF-β1 pathway to regulate or inhibit its constitutive activation of MDS progenitors have been reported for the treatment of MDS. Furthermore, TGF-β1 plays a central role in tumor development by facilitating the extravasation of metastasizing tumor cells. These data suggest that TGF-β1, which is produced by cancer cells and skin cells (eg, fibroblasts, immune cells), is able to create a microenvironment that promotes the induction of cancer cell migration and GS formation, thereby explaining the KP.

The spontaneous regression of the 2 GSs in this case may be explained by the negative feedback of the amplification loop operated by TGF-β1 or normalization of the TGF-β1 pathway during the skin wound healing process. The exact role of TGF-β1 and its specific receptor remains to be clearly elucidated.

REFERENCES

1. Hurley MY, Ghalramani GK, Frisch S, et al. Cutaneous myeloid sarcoma: natural history and biology of an uncommon manifestation of acute myeloid leukemia. Acta Derm Venereol. 2013;93(3):319-324.
2. Collie AM, Uchin JM, Bergfeld WF, Billings SD. Cutaneous intravascular extramedullary hematopoiesis in a patient with post-polycythemia vera myelofibrosis. J Cutan Pathol. 2013;40(7):615-620.
3. Patel LM, Maghari A, Schwartz RA, Kapilla R, Morgan AJ, Lambert WC. Myeloid leukemia cutis in the setting of myelodysplastic syndrome: a crucial dermatological diagnosis. Int J Dermatol. 2012;51(4):383-388.
4. Kawakami T, Kimura S, Kato M, Mizoguchi M, Soma Y. Transforming growth factor-beta overexpression in cutaneous extramedullary hematopoiesis of a patient with myelodysplastic syndrome associated with myelofibrosis. J Am Acad Dermatol. 2008;58(4):703-706.
5. Avivi I, Rosenbaum H, Levy Y, Rowe J. Myelodysplastic syndrome and associated skin lesions: a review of the literature. Leuk Res. 1999;23(4):323-330.
6. Weiss G, Shemer A, Trau H. The Koebner phenomenon: review of the literature. J Eur Acad Dermatol Venereol. 2002;16(3):241-248.
7. Nafil H, Tazi I, Mahmal L. Myeloid sarcoma developing in preexisting hydroxyurea-induced leg ulcer in a polycythemia vera patient. Case Rep Med. 2013;2013:97593.
8. Sen R, Singh S, Qury MS, Manwah S, Aggarwal G, Singla S. Chloroma of perianal region masquerading as perianal abscess. Indian J Dermatol. 2013;58(1):85.
syndrome: “pseudo-Koebner phenomenon”. J Clin Pathol. 1998;51(11):860-861.

10. Byrd JC, Edenfield WJ, Dow NS, Aylesworth C, Dawson N. Extramedullary myeloid cell tumors in myelodysplastic-syndromes: not a true indication of impending acute myeloid leukemia. Leuk Lymphoma. 1996;21(1-2):153-159.

11. Principe DR, Doll JA, Bauer J, et al. TGF-β: duality of function between tumor prevention and carcinogenesis. J Natl Cancer Inst. 2014;106(2):djt369.

12. Bhagat TD, Zhou L, Sokol L, et al. miR-21 mediates hematopoietic suppression in MDS by activating TGF-β signaling. Blood. 2013;121(15):2875-2881.