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Unique Recognizable Histopathologic Variant of Palisaded Neutrophilic and Granulomatous Dermatitis that Is Associated With SRSF2-Mutated Chronic Myelomonocytic Leukemia: Case Report and Review of the Literature

Christina D. Enescu
Henry Ford Health, cenescu1@hfhs.org

Avni Patel
Henry Ford Health, apatel47@hfhs.org

Ben J. Friedman
Henry Ford Health, bfriedm1@hfhs.org

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Unique Recognizable Histopathologic Variant of Palisaded Neutrophilic and Granulomatous Dermatitis that Is Associated With SRSF2-Mutated Chronic Myelomonocytic Leukemia: Case Report and Review of the Literature

Christina D. Enescu, BS, Avni Patel, MD,† and Ben J. Friedman, MD†‡*

Abstract: Palisaded neutrophilic and granulomatous dermatitis (PNGD) represents a cutaneous histopathologic reaction spectrum associated with several underlying disorders. Few cases of PNGD have been associated with chronic myelomonocytic leukemia (CMML), a malignant hematopoietic disorder with features in between those of a myeloproliferative neoplasm and myelodysplastic syndrome. We present a patient with a generalized papular skin reaction involving the neck, chest, and shoulders with histomorphological features on the spectrum of PNGD. Subsequent laboratory workup demonstrated a persistent mild monocytosis, raising concern for CMML. The diagnosis was ultimately confirmed with a bone marrow biopsy and associated mutational analysis through next-generation sequencing which identified deleterious variants in SRSF2, IDH2, and ASXL1. The findings in this case strengthen the previously made association between PNGD and SRSF2-mutated CMML and may help better define a unique recognizable clinical–histopathological–molecular subtype for dermatopathologists.

Key Words: palisaded neutrophilic and granulomatous dermatitis, chronic myelomonocytic leukemia, granulomatous dermatitis, monocytosis, SRSF2

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INTRODUCTION

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is a rare cutaneous histopathologic reaction pattern that has been associated with several underlying systemic disorders including rheumatoid arthritis, connective tissue diseases such as systemic lupus erythematosus, certain drugs, and hematologic malignancies. The etiology of PNGD is largely unknown, but it is believed to be driven by a systemic inflammatory pathway given its varied internal disease associations.[1] The exact definition/usage of the term PNGD has been a source of confusion in previous literature, especially as it relates to a similar disorder interstitial granulomatous dermatitis (IGD). Rosenbach et al 2015 proposed the term "reactive granulomatous dermatitis" to encompass both conditions which may have varied clinical and histopathologic features yet maintain the same general disease associations.

The association between PNGD and hematologic malignancies, particularly chronic myelomonocytic leukemia (CMML), is rare with only a few scattered reports in the literature.[2,3] CMML is a malignant hematopoietic disorder with features of a myeloproliferative neoplasm and myelodysplastic syndrome.[4] Peripheral blood monocytosis and bone marrow dysplasia characterize this form of leukemia, which may also be accompanied by cytopenias and splenomegaly. In cases where dysplasia is absent or minimal, the diagnosis of CMML can be supported by an acquired clonal cytogenetic abnormality most commonly in *TET2, SRSF2, ASXL1, RUNX1, NRAS,* and *CBL*. In this case, we provide an in-depth description of a peculiar skin eruption with histomorphological features on the spectrum of PNGD that ultimately led to a diagnosis of CMML. The findings in this case strengthen the previously made association between PNGD and SRSF2-mutated CMML and may help better define a unique recognizable subtype.

CASE REPORT

A 76 year-old woman with a medical history significant for coronary artery disease, mild cognitive impairment, and shingles presented with a diffuse painful skin eruption affecting her ears, neck, upper chest, upper back, extensor arms, and forearms (Fig. 1). The rash had been slowly progressive over 8 months, with pertinent negatives including no mucosal involvement or preceding medication changes. Physical examination revealed primary lesions consisting of clusters of firm coalescing erythematous to yellow–brown papules (some in an annular configuration) with central hyperpigmentation. Few lesions at the leading edges had some overlying scale.

Punch biopsies were taken from the left arm (Figs. 2 and 3) and right upper back (Figs. 4 and 5) and revealed similar findings. Sections demonstrated a top-heavy wedge-shaped granulomatous inflammatory infiltrate centered on the upper dermis. Smaller granulomas were seen in a perivascular and periadnexal pattern in the deeper portions of the reticular dermis. The epidermis was unremarkable with a thin grenz zone appreciated. The infiltrate consisted of a layered arrangement of epithelioid histiocytes (many multinucleated and a large proportion foamy to varying degrees) peppered with considerable neutrophils and fewer lymphocytes. Occasional pockets of degenerate collagen studded with karyorrhectic debris were identified. Alcian blue stain was negative for increased dermal mucin.

From the *Wayne State University School of Medicine, Detroit, MI; †Department of Dermatology, Henry Ford Health System, Detroit, MI; and ‡Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI.

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Correspondence: Ben J. Friedman, MD, Department of Dermatology, Henry Ford Health System, 3031 W. Grand Boulevard, Suite 800 Detroit, MI 48202 (e-mail: bfriedm1@hfhs.org).

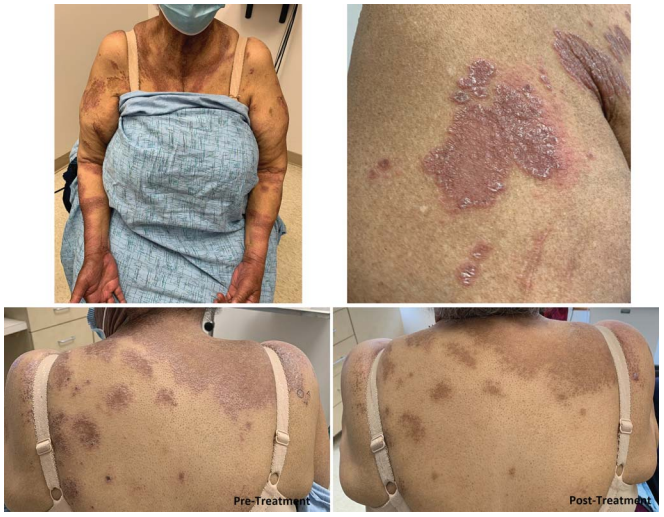

FIGURE 1. Clinical photographs. Diffuse red–brown papular eruption involving trunk and extremities. Some lesions have focal overlying scale. Only residual macular hyperpigmentation is seen after treatment (lower right hand corner).

Various granulomatous conditions including necrobiotic xanthogranuloma and granuloma annulare were considered in the differential diagnosis, although reactive granulomatous dermatitis (PNGD-like pattern) was ultimately favored. The presence of considerable neutrophils, foamy change, and lack of mucin made granuloma annulare less likely while the distinctly top-heavy wedge-shaped configuration of the infiltrate and focal nature of the necrobiosis were not typical of necrobiotic xanthogranuloma.

A broad laboratory workup was pursued based on the above findings which included a complete blood count, comprehensive metabolic panel, lipid profile, angiotensin-converting enzyme, QuantiFERON-TB gold assay, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, rheumatoid factor, rapid plasma reagin, chest x-ray, and both serum protein electrophoresis and urine protein electrophoresis. Test results were normal except for an elevated absolute monocyte count of 1.40 K/μL, a mild normocytic anemia with a hemoglobin of 11.8 g/d, and an elevated erythrocyte sedimentation rate of 57 mm/hr. On further chart review, it was noted that the patient had a chronically elevated absolute monocyte count dating back at least 3 years, ranging from 1.30 to 2.5 K/μL and a monocyte % consistently >10.

The constellation of findings raised some concern for a myeloproliferative disorder, and therefore, the patient was referred to hematology–oncology. Bone marrow biopsy was performed and showed hypercellularity with mild megakaryocytic dysplasia, less than 5% ringed sideroblasts on an iron stain, and no increase in blast cells. No cytogenetic abnormalities were found on a myelodysplastic syndrome fluorescence in situ hybridization panel. A hematolymphoid 51-gene next-generation sequencing panel detected 3 pathogenic mutations (high frequency) including IDH2 R140Q, SRSF2 P95H, and ASXL1 R965, which strongly supported the diagnosis of CMML in the context of minimal myelodysplasia. After discussion at a multidisciplinary tumor board, treatment directed at the skin eruption alone was recommended. She was started on prednisone taper and demonstrated marked clinical improvement (Fig. 1, right lower panel).

DISCUSSION

Chu et al[5] 1994 first coined the term "PNGD" to describe a histopathologic reaction pattern occurring in the setting of collagen vascular disease. In that initial report, PNGD was characterized as a pan-dermal diffuse process that starts as a small-vessel leukocytoclastic vasculitis with necrobiotic collagen which then progresses to palisaded granulomas and dermal fibrosis. In subsequent literature, the concept of "IGD" was developed which demonstrated similar systemic clinical associations as for PNGD, although arguably with slightly different clinical presentations and histomorphologic features.[6,7] IGD reportedly comprised a diffuse dermal inflammatory infiltrate composed mostly of histiocytes distributed interstitially and in palisaded array within the reticular dermis. Additional findings included few bundles of degenerated collagen with few surrounding neutrophils and eosinophils.

Larger more recent series on the topic of PNGD and IGD have illustrated the difficulty in trying to distinguish between these 2 entities. An argument has been made for inclusion of PNGD and IGD under the same general category of reactive granulomatous dermatitis (RGD) which may potentially simplify things for clinicians and dermatopathologists.[1,8] In these larger series, autoimmune diseases, collagen vascular disorders, and drugs are consistently identified as the strongest association with RGD, with hematologic malignancies representing only a minority of cases.[1,8] It remains to be seen whether there are reliable clinical and histomorphologic features in this spectrum of RGD that could help predict the presence of specific underlying disorders on a case-to-case basis.

On review of the literature, there have been 4 previous reports of PNGD occurring in the context of CMML.[3] Our case is noteworthy because it has a striking similarity to 3 patients described in detail by Federman et al 2017 in which a diagnosis of PNGD preceded identification of underlying

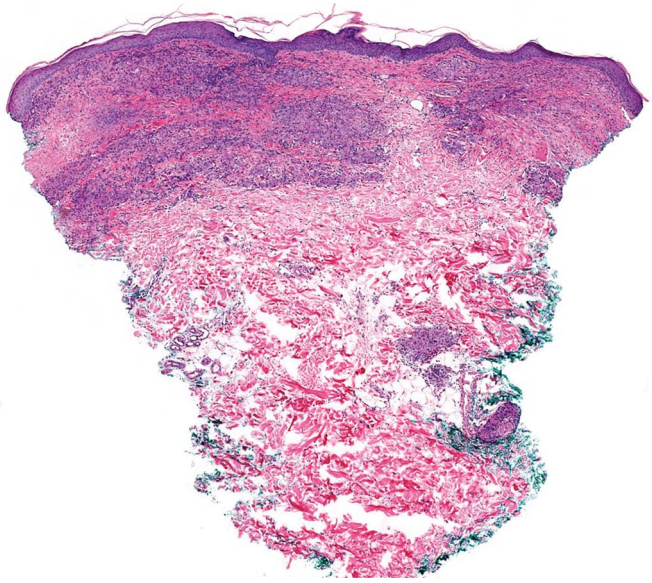

FIGURE 2. Left arm. Low-power histopathology: There is a subepidermal lichenoid to wedge-shaped infiltrate with a predominance of pale staining histiocytes (H&E, ×40, original magnification).

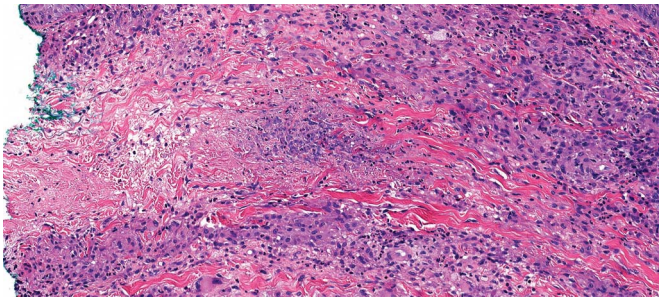

FIGURE 3. Left arm. High-power histopathology: Layered collections of histiocytes forming granulomas are seen surrounding a central area of degenerate collagen. Considerable numbers of neutrophils are seen admixed with the histiocytes and also in the central necrobiotic zone with occasional karyorrhexis (H&E, ×200, original magnification).

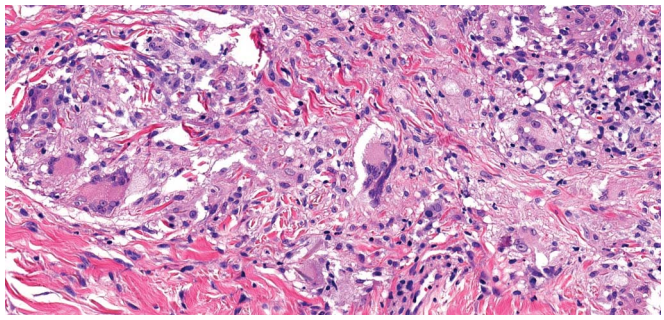

FIGURE 5. Right upper back. High-power histopathology: Collections of histiocytes with multiple multinucleated cells containing foamy cytoplasm. Few admixed neutrophils and lymphocytes are identifiable (H&E, ×300, original magnification).

CMML. All patients in that series presented with a widespread erythematous to brown papular eruption involving the trunk and extremities. Interestingly, skin biopsies from all 3 patients mirrored the findings observed in our case. Specifically, infiltrates were characterized by collections of histiocytes arranged in a subepidermal/top-heavy lichenoid configuration with variably intermingled neutrophils and lymphocytes. Neutrophils were seen in a random interstitial pattern but also around vessels. Not specifically mentioned by the authors (although readily discernible in the published photomicrographs of the skin biopsies in their publication) was that many of the histiocytes were multinucleate and contained foamy cytoplasm, which we too observed in our case.[2] Foamy change is not commonly emphasized in the multitude of other reported cases of RGD occurring in other contexts.[1,8] Necrobiotic collagen as seen focally in 1 of our patients biopsies was also noted in 1 of 3 of their cases. Further similarities between our case and the patients in the study by Federman et al 2017 included a concomitant (initially overlooked) low-grade monocytosis and ultimate detection of an SRSF2 mutation on bone marrow biopsy (2/3 with identical p.P95H).

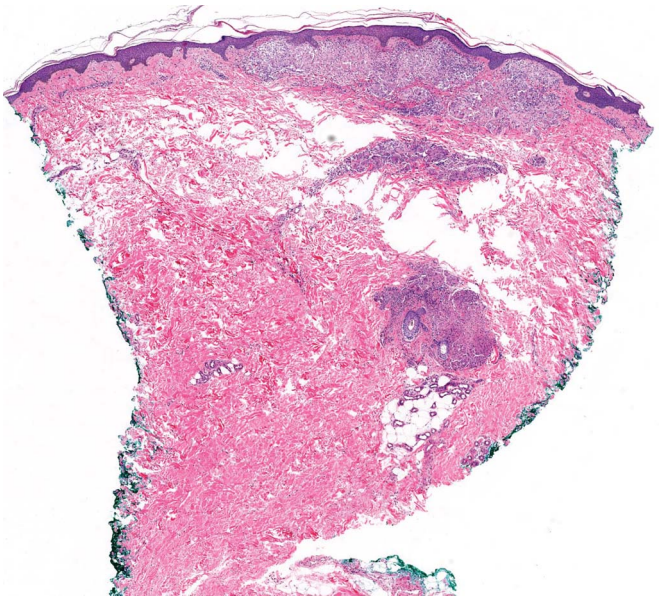

FIGURE 4. Right upper back. Low-power histopathology: There is a subepidermal lichenoid to wedge-shaped infiltrate with a predominance of pale staining histiocytes. There is a prominent perifollicular component in the deeper portion (H&E, ×40, original magnification).

In summary, we report the fifth case of so-called PNGD preceding a diagnosis of CMML, the fourth having a confirmed underling SRSF2 mutation. The findings here replicate those of Federman et al 2017 and bring attention to what is likely a novel and reproducible clinical–histopathological–molecular subtype of RGD that dermatopathologists should be aware of. Notable features of this entity include an elderly patient with a diffuse/generalized firm papular eruption of the trunk and extremities, which on skin biopsy will show a dense top-heavy wedge-shaped dermal infiltrate of histiocytes, many being multinucleate and foamy. There are considerable admixed neutrophils and occasional lymphocytes, with focal areas of necrobiotic collagen that may become more apparent on serial sectioning. The constellation of these features should prompt review of serial complete blood counts with differentials to detect a chronically elevated monocyte count. The exact pathophysiology underlying this association is unclear, although may be related to the SRSF2 mutation detected in our case and that in the study by Federman et al 2017. In the absence of other hematologic abnormalities, systemic steroids or methotrexate may be a good short-term treatment option for these patients, although longer-term follow-up and larger case series are needed to replicate these findings. Although we agree that the concept of RGD may simplify what is undoubtedly a complicated spectrum of disorders, we believe that this particular variant may be best separated out as a distinct clinical entity given its uniquely consistent features.

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