

Nevus anemicus: An island of sparing in the setting of drug-induced hypersensitivity



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INTRODUCTION

Nevus anemicus (NA) is an uncommon congenital finding characterized by a discrete area of hypopigmentation that remains stable in size throughout life. To our knowledge, generalized cutaneous eruption sparing NA in a mosaic fashion has never been reported in the literature. We report a case of erythrodermic drug-induced hypersensitivity syndrome (DIHS) in the setting of human herpes 6 virus (HHV-6) viremia, sparing NA.

CASE

A 72-year-old woman with a complex medical history including double lung transplant, chronic kidney disease, and partial hepatectomy was transferred from an outside hospital for further evaluation of a liver abscess.

Seven days before transfer, the patient presented to a local hospital with fever to 104°F and leukocytosis of $40 \times 10^3/\mu\text{L}$. She was subsequently found to have a large liver abscess and streptococcus bacteremia. The patient was started on vancomycin, aztreonam, levofloxacin, and metronidazole and was transferred to Columbia University for complex medical management.

Upon arrival, the patient's antibiotics were narrowed to ceftriaxone and metronidazole. She was maintained on her longstanding transplant medications including mycophenolate mofetil, cyclosporine, prednisone, and trimethoprim/sulfamethoxazole.

Abbreviations used:

DIHS:	drug-induced hypersensitivity syndrome
HHV-6:	human herpes 6 virus
NA:	nevus anemicus
NDP:	nevus depigmentosus

On day 29 of hospitalization, a pruritic lacy red rash developed that was limited to the chest. Infection workup found HHV-6 viremia of 37,000 DNA copies per milliliter, and she was started on valganciclovir. The rash gradually progressed to cover her entire body, and the dermatology department was consulted for evaluation on day 40 of hospitalization.

On physical examination, the patient had generalized blanching erythema covering the trunk and extremities. The face and a discrete 5-cm hypopigmented patch on the upper back were spared (Fig 1). Upon rubbing the skin within the hypopigmented patch, reactive erythema was not observed. The pale patch was reportedly present since birth and had remained stable in size, consistent with NA. Laboratory values included a white blood cell count of $5.02 \times 10^3/\mu\text{L}$ with marked eosinophilia of 14.9%, creatinine value of 2.01 mg/dL (baseline, 1.3 mg/dL), absent transaminitis (aspartate aminotransferase, 11 U/L; alanine aminotransferase, 8 U/L; alkaline phosphatase, 130 U/L), and HHV-6 titers of 18,000 DNA copies per milliliter. Punch biopsy of the rash

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Fig 1. Generalized morbilliform rash sparing NA.

showed perivascular dermatitis consistent with a dermal hypersensitivity reaction (Fig 2). Medication history implicated ceftriaxone as the likely culprit, leading to its discontinuation and resolution of the rash within 9 days.

DISCUSSION

DIHS is an idiosyncratic reaction to variety of drugs. Although the pathogenesis of cutaneous drug eruptions in the setting of viral infections remains poorly understood, a growing list of viruses has been linked to the development of a drug-specific immune reactions. In particular, HHV-6 has been increasingly associated with the development of DIHS.¹ Previous studies temporally correlated the magnitude of HHV-6 viremia with disease severity, suggesting HHV-6 as the trigger for DIHS, rather than disease sequelae.²

NA is a congenital, nonprogressive skin anomaly that typically presents as an isolated, well-defined, hypopigmented, irregularly shaped, patch on the trunk.³ Although NA is not usually associated with other abnormalities, it has been linked to several conditions including neurofibromatosis type I and phacomatosis pigmentovascularis.^{4,5} Although the differential diagnosis for NA includes common conditions such as vitiligo and tinea versicolor, it also includes nevus depigmentosus (NDP), a cutaneous lesion that shares many clinical features with NA.

Differentiating NA from NDP can be challenging. Like NA, NDP is a rare cutaneous anomaly that most commonly presents at birth as a hypopigmented patch; however, simple physical examination techniques can be used to make the diagnosis.⁶ In this case, NA was distinguished from NDP, as no erythema was observed in the hypopigmented area after being rubbed. Had the hypopigmented patch been that of NDP, one would expect to see an erythematous mark at the site of mechanical stimulation.³

The dichotomous physical examination findings of NDP and NA primarily reflect their differences in

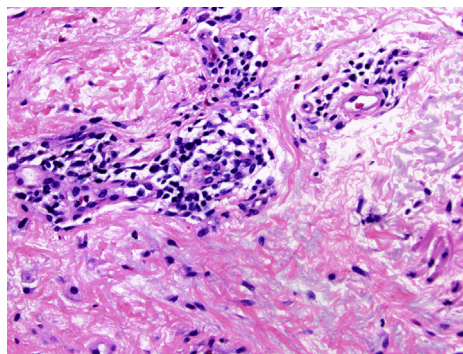


Fig 2. Hematoxylin and eosin–stained section of the punch biopsy specimen shows a perivascular infiltrate of lymphocytes and scattered eosinophils.

pathogenesis. NDP is caused by melanocyte dysfunction that results in decreased synthesis of melanosomes.⁶ In contrast, NA is believed to arise from focal blood vessel hypersensitivity to catecholamines, leading to persistent vasoconstriction and skin pallor.⁷ The pathomechanistic hypothesis of NA has been supported by several pharmacologic studies that showed restoration of normal skin coloration after intralesional sympathetic blockade.⁷ Given the pathophysiologic decrease in blood flow under vasoconstrictive conditions, it is thus not entirely surprising that NA would be spared in generalized drug rash. However, sparing phenomenon in the setting of generalized drug rash remains a poorly understood entity and has been reported in only a handful of cases including sparing of a leprosy macule in ampicillin hypersensitivity rash, sparing of leprosy patch in dapsone hypersensitivity syndrome, nafcillin-related leukocytoclastic vasculitis sparing a tattoo, and phenobarbital drug rash sparing NDP.⁸⁻¹¹ Of previously reported cases, local immune dysfunction was consistently posited as a potential pathophysiologic mechanism of skin disease sparing. Therefore, sparing of NA may be more complex than what available research suggests.

Although the mechanistic basis of cutaneous sparing in NA appears to be relatively straightforward, it is possible that local immune dysregulation may here too be a contributing factor. In one previous study, histologic evaluation of biopsies obtained from a patient with generalized contact dermatitis sparing NA found the absence of an inflammatory cell infiltrate within the NA lesion.¹² In contrast to the surrounding skin, NA dermal microvessels were negative for E-selectin, and epidermal keratinocytes were negative for ICAM-1 and HLA-DR – consistent with the absence of immunologically reactive cytokines. To better understand these findings, interferon- γ was injected into NA and normal adjacent

skin in a patient with no inflammatory skin disease. Histopathologic evaluation of preinjection and post-injection of lesional and adjacent skin was notable for persistent lack of E-selectin expression within NA. Because HLA-DR and ICAM-1 were both upregulated in NA by interferon- γ , a defective cytokine response is suggested to be at the level of the endothelial cell, not the keratinocyte.¹² Therefore, both adrenergic hypersensitivity and impaired immune responsiveness may have additive effects in producing an area of sparing. Although the role of HHV-6 is not well understood in this case, it is possible that HHV-6 infection may also be relevant to local immune dysfunction and skin sparing. Further investigation to the possible correlation between HHV-6 viremia, DIHS, and dysregulation of the immune microenvironment in sparing phenomenon is warranted.

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