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Citation
Young, Grace J., Nicole Harter, and Minnelly Luu. 2016. “An unusual migratory polycyclic eruption after administration of prostaglandin E in a neonate.” JAAD Case Reports 2 (5): 377-379. doi:10.1016/j.jdcr.2016.08.001. http://dx.doi.org/10.1016/j.jdcr.2016.08.001.

Published Version
doi:10.1016/j.jdcr.2016.08.001

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CASE REPORT

An unusual migratory polycyclic eruption after administration of prostaglandin E in a neonate

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Key words: alprostadil; congenital heart disease; prostaglandin E; rash; urticarial.

INTRODUCTION

Alprostadil is a prostaglandin E1 analogue (PGE1 α-cyclodextrin clathrate) used in neonates to maintain a patent ductus arteriosus in cases of ductal-dependent congenital heart disease (CHD).1 PGE1 is critical in sustaining oxygen saturation in these patients while awaiting surgical repair or cardiac transplant. Despite being reasonably well tolerated, a review of 62 neonates with CHD treated with PGE1 suggested a range of adverse events, most commonly including central nervous system events (16%), respiratory depression (12%), and cardiovascular complications (18%).2

Cutaneous flushing and peripheral edema are well-recognized side effects of PGE1 infusion,2 although there is a paucity of data with regard to cutaneous adverse events. A search of the literature found 4 other cutaneous reactions reported, including harlequin color change, urticaria, and subcutaneous fat necrosis of the newborn.3-5 We present a case of an extensive and striking polycyclic eruption associated with PGE1 administration in a 2-day-old neonate and highlight the importance of recognizing this entity to avoid delay in diagnosis and unnecessary interventions.

CASE REPORT

A full-term male neonate with prenatally diagnosed severe congenital diaphragmatic hernia was intubated at birth and transferred to our institution for surgical management of the condition and extracorporeal membrane oxygenation (ECMO), which was started on day 2 of life. An echocardiogram obtained before ECMO was significant for dilated right-sided cardiac structures and a large patent ductus arteriosus with right-to-left shunt. The patient’s medications included dopamine, sildenafil, alprostadil, fentanyl, ampicillin, gentamycin, and heparin.

On day 3 of life, a widespread erythematous eruption developed on the patient’s trunk and extremities for which the dermatology department was consulted. The eruption was minimally responsive to diphenhydramine. Examination found brightly erythematous annular and polycyclic patches on the face, trunk, and extremities, which were noted to migrate throughout the day, sometimes within minutes (Fig 1). There was periangual erythema of similar quality, and the upper eyelids were erythematous and edematous. Mucous membranes were intact. The patient was afebrile. The differential diagnosis included urticaria, drug eruption, or an urticarial eruption associated with an autoinflammatory syndrome such as neonatal-onset multisystem inflammatory disease. Skin biopsy was offered but declined by the family.

Because of the possibility of a drug reaction, close observation was performed over the ensuing 24 hours, and the rash appeared to be exacerbated.

Abbreviations used:

CHD: congenital heart disease
ECMO: extracorporeal membrane oxygenation
PGE1: prostaglandin E1

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Funding sources: None.
Conflicts of interest: None declared.
This case was presented at the 28th Annual Society for Pediatric Dermatology Pre-AAD Meeting in Washington, DC, on March 3, 2016.
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JAAD Case Reports 2016;2:377-9.
2352-5126
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http://dx.doi.org/10.1016/j.jdcr.2016.08.001

http://dx.doi.org/10.1016/j.jdcr.2016.08.001

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by administration of alprostadil. To establish this connection, PGE1 was held on day 4 of life with complete resolution of the rash within minutes of discontinuation (Fig 2). To further support this association, alprostadil was rapidly restarted, with immediate recurrence of the rash. Given the unclear significance of this widespread eruption, PGE1 was discontinued. However, flow rates on ECMO were compromised immediately after removal of PGE1; on day 8 of life PGE1 was reinitiated, interestingly without recurrence of the rash.

**DISCUSSION**

In this case, a 2-day-old neonate experienced a migratory, annular cutaneous eruption after administration of PGE1. To our knowledge, this is a very rare reported side effect of PGE1 administration, with 1 similar case reported in the literature.3

Dermatologic complications after PGE1 administration are currently poorly characterized, particularly in pediatric cohorts. A review of the literature found 4 reports of cutaneous reactions after PGE1 administration for CHD, including harlequin color change, urticaria, and subcutaneous fat necrosis of the newborn,3-5 with all instances occurring in neonates. Carter and Garzon3 described a migratory polycyclic erythema after starting alprostadil in a neonate, and biopsy in this case was consistent with urticaria. A review of pediatric annular lesions by Nopper et al6 noted the occurrence of transient annular erythema in neonates receiving intravenous prostaglandins, whereas Rao et al1 reported harlequin color change in 3 neonates associated with PGE1 administration.

PGE1 is proposed to induce cutaneous inflammation viavasodilation, leading to local edema and hyperemia. Interestingly, the reported case lacked an edematous component. The severity of the response—both in this and prior cases3—was directly correlated with the amount of PGE1 administered. This finding suggests a nonallergic mechanism, as allergic responses generally do not exhibit a direct dose-response relationship, with even minimal quantities inducing life-threatening symptoms.

Administration of PGE1 may elicit vasodilation via a nonallergic pathway of histamine release analogous to the “red man syndrome” of vancomycin, an anaphylactoid reaction that induces direct degranulation of mast cells and basophils without preformed IgE or complement. Factors known to modulate severity of red man syndrome include dose and rate of infusion, with severity generally improving with slower infusion.8 A number of experimental trials found PGE1’s ability to trigger release of histamine from mast cells and basophils and elicit dose-correlative cutaneous events.7,8 These events may also be analogous to nonallergic urticaria in which mast cells undergo direct degranulation, a process well described with medications including opioids and nonsteroidal anti-inflammatory drugs.9
Although intradermal PGE1 injection is known to cause a dose-dependent wheal and flare reaction, the wheal—but not the flare—is suppressed by antihistamine pretreatment.8 This finding argues that histamine is unlikely to be the sole mediator in the pathogenesis of this reaction, further suggesting that PGE1 may lead to vasodilation and cutaneous inflammation via concurrent mechanisms independent of histamine, as in bradykinin-induced angioedema. Newer data suggest involvement of the coagulation cascade in the pathogenesis of chronic urticaria, with thrombin inducing mast cell activation and production of anaphylatoxin C5a.10,11 Metz et al12 have also described increased levels of neuropeptide substance P in patients with chronic urticaria. It is not known if PGE1 may alter these pathways. Notably, our patient did not benefit from treatment with diphenhydramine, which aligns with the findings in previously reported cases and further argues against a pathogenesis solely related to histamine.8

Neonatal hypoxia has been proposed to underlie the pathogenesis of harlequin color change13 and subcutaneous fat necrosis of the newborn. PGE1 is administered to infants with cyanotic CHD.1 Overall, this finding may suggest an underlying theme in which hypoxic events early in life engender a predisposition toward aberrant vasodilatory cutaneous reactions in these patients, which may also involve thrombin and alteration of the coagulation cascade.11,12

A migratory, polycyclic erythema may occur in neonates exposed to PGE1. In particular, this symptomology seems to accompany hypoxia in the setting of CHD, and we hypothesize that previously reported cases of harlequin color change and urticaria may also represent aberrant vasodilatory responses. Recognition of this striking cutaneous side effect allows for expedient diagnosis and avoidance of unnecessary interventions. Given the lack of systemic sequelae thus far reported, interruption of treatment may not be necessary in all cases and continuation carefully considered when PGE1 is a life-sustaining therapy. Future studies may lead to additional corroboration and greater understanding of the biochemical mechanism of this obscure event.

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