Annular Erythema of Infancy With Reactive Helper T Lymphocytes

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PRACTICE **POINTS**

- Annular erythemas of infancy (AEIs) are rare benign skin eruptions characterized by persistent, annular, urticarial, nonpruritic patches and plaques that develop in patients younger than 1 year.
- Although AEIs are benign, lesions with uncommon histologic features such as large mononuclear cells consistent with reactive helper T lymphocytes may pose diagnostic challenges.

Annular erythemas of infancy (AEIs) are rare benign skin eruptions characterized by persistent, annular, urticarial, nonpruritic patches and plaques that develop in patients younger than 1 year. Histologically, a skin biopsy typically demonstrates a perivascular infiltrate in the dermis composed of small lymphocytes, neutrophils, and increased scattered eosinophils. We report a case of an AEI in an 11-month-old girl with uncommon histologic features. Recognition of these benign cells is important to avoid misdiagnosing them as atypical or neoplastic. We also provide a review of the differential diagnosis for AEIs.

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Annular erythemas of infancy (AEIs) are rare benign skin eruptions characterized by annular or circinate, erythematous patches and plaques that arise in patients younger than 1 year.[1] Annular erythemas of infancy originally were described by Peterson and Jarratt[2] in 1981. Relatively few cases of AEIs have been reported in the literature (eTable).[2-15]

Case Report

An 11-month-old girl presented to dermatology for a rash characterized by annular erythematous patches and plaques on the back, arms, and legs (Figure 1). Three months prior, the rash was more diffuse, monomorphic, and papular. Based on physical examination, the differential diagnosis included a gyrate erythema such as erythema annulare centrifugum (EAC), neonatal lupus, a viral exanthem, leukemia cutis, and AEI. A skin punch biopsy was performed.

Histologically, the biopsy revealed a superficial to mid dermal, tight, coat sleeve–like, perivascular lymphohistiocytic infiltrate admixed with rare neutrophils in eosinophils within the dermis (Figure 2A). The infiltrate also contained numerous large mononuclear cells with enlarged nuclei, fine loose chromatin, rare nucleoli, and a thin rim of cytoplasm (Figure 2B). There were associated apoptotic bodies with karyorrhectic debris. Immunohistochemistry exhibited enlarged cells that were strong staining with CD3 and CD4, which was consistent with reactive helper T cells (Figure 3). A myeloperoxidase stain highlighted few neutrophils. Stains for terminal deoxynucleotidyl transferase, CD1a, CD117, and CD34 were negative. These findings along with the clinical presentation yielded a diagnosis of AEI with reactive helper T cells.

Comment

Clinical Presentation of AEIs—Annular erythemas of infancy are rare benign skin eruptions that develop in the first few months of life.[1,16] Few cases have been reported (eTable). Clinically, AEIs are characterized by annular or circinate, erythematous patches and plaques. They can occur on the face, trunk, and extremities, and they completely resolve by 1 year of age in most cases. One case was reported to persist in a patient from birth until 15 years of age.[9] It is thought that AEIs may occur as a hypersensitivity reaction to an unrecognized antigen.

Histopathology—Histologically, AEIs demonstrate a superficial and deep, perivascular, inflammatory infiltrate in the dermis composed of small lymphocytes, some neutrophils, and eosinophils.[16] Less common variants of AEI include eosinophilic annular erythema, characterized by a diffuse dermal infiltrate of eosinophils and some lymphocytes, and neutrophilic figurate erythema of infancy, characterized by a dermal infiltrate with neutrophils and leukocytoclasis without vasculitis.[1]

Our patient's skin rash was unusual in that the biopsy demonstrated few neutrophils, rare eosinophils, and larger mononuclear cells consistent with reactive helper

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.
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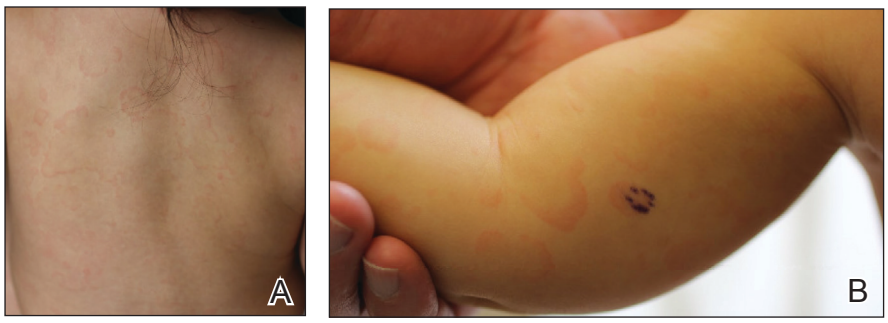

FIGURE 1. A, An 11-month-old girl with annular erythematous patches and plaques on the back. B, Annular erythematous lesions were present on the right arm, from which a punch biopsy was taken.

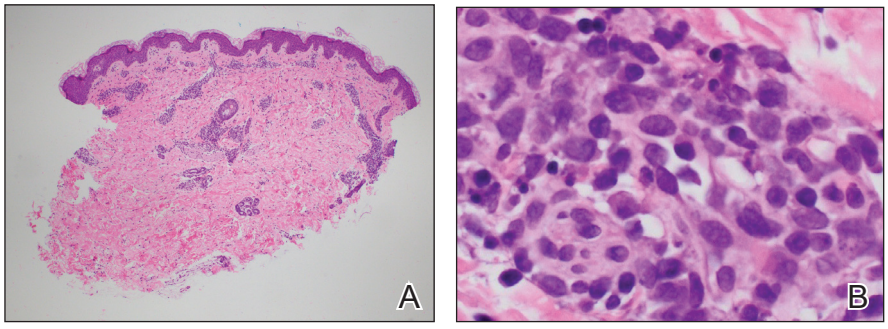

FIGURE 2. Histopathology demonstrated annular erythema of infancy with mononuclear cells. A, There was a superficial to mid dermal, tight, coat sleeve–like, perivascular, lymphohistiocytic infiltrate admixed with rare neutrophils in eosinophils within the dermis (H&E, original magnification ×40). B, The infiltrate contained numerous large mononuclear cells with enlarged nuclei, fine loose chromatin, rare nucleoli, and a thin rim of cytoplasm (H&E, original magnification ×400).

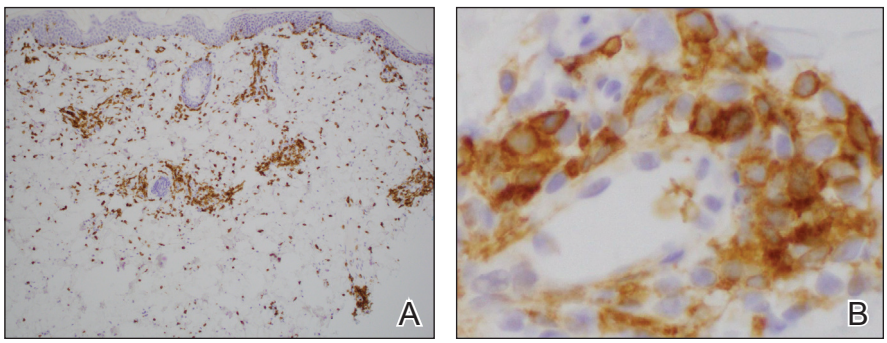

FIGURE 3. A, Immunohistochemistry revealed the infiltrate was composed predominantly of $CD3^+$ T lymphocytes (original magnification ×100). B, The enlarged cells were $CD4^+$, consistent with reactive helper T cells (original magnification ×400).

T lymphocytes. Although these cells may raise concern for an atypical lymphoid infiltrate, recognition of areas with more conventional histopathology of AEIs can facilitate the correct diagnosis.

Differential Diagnosis—The main considerations in the differential diagnosis for AEIs include the following: EAC, familial annular erythema, erythema gyratum atrophicans transiens neonatale, erythema chronicum migrans, urticaria, tinea corporis, neonatal lupus erythematosus, viral exanthems, and leukemia cutis.[16]

Erythema annulare centrifugum typically begins in middle age and follows a course of 2 or more years.[2] It occurs in association with an underlying infection or neoplasm, and it can develop on the trunk and proximal extremities. Morphologically, EAC can present with arcuate or polycyclic lesions with trailing scale. Histologically, a skin biopsy shows a tight, coat sleeve–like, perivascular, lymphohistiocytic infiltrate in the dermis, with variable epidermal spongiosis and parakeratosis.[16] Our patient's biopsy did show a tight perivascular infiltrate, raising suspicion for EAC. However, the eruption occurred in infancy, and she had no clinical evidence of infection or neoplasm.

Familial annular erythemas can arise within a few days after birth and can present on any part of the body, including the tongue.[2] Individual lesions can persist for 4 to 5 days and can accompany congenital malformations. Morphologically, they can present as papules that slowly enlarge to form arcuate lesions with central hyperpigmentation. Histologically, there can be a mild, perivascular, lymphocytic infiltrate in the dermis.[16] Our patient's lesions showed no scale or pigmentation and occurred without a family history or associated malformations.

Erythema gyratum atrophicans transiens neonatale also can arise in the first few days of life and can affect the trunk, neck, and lips.[16] Morphologically, the skin lesions can present as arcuate erythematous patches (3–20 mm) with raised borders and central atrophy. Histologically, there is epidermal atrophy with a dermal perivascular mononuclear cell infiltrate with edema. Our patient's clinical presentation was not classic for this condition, and the lesions showed no atrophy.

Erythema chronicum migrans can arise in children, often with a history of an arthropod bite.[13] Morphologically, lesions can evolve over weeks to months and rarely are multiple.

Erythema chronicum migrans most commonly occurs in the United States in association with Lyme disease from infection with *Borrelia burgdorferi*. Histologically, erythema chronicum migrans shows a superficial and deep, perivascular lymphocytic infiltrate in the dermis with plasma cells and eosinophils. A silver stain can demonstrate dermal spirochetes. Our patient had no history of an arthropod bite. A Warthin-Starry stain performed on the biopsy was negative for spirochetes, and serologies for Lyme disease were negative.

Urticaria is rare in neonates and can occur on any part of the body.[2] Morphologically, the skin lesions can present as arcuate, erythematous, and polycyclic plaques that wax and wane. Histologically, there is dermal edema with a mild, perivascular and interstitial, mixed inflammatory infiltrate.[16] Our patient's biopsy did not reveal notable edema, and the perivascular infiltrate was coat sleeve–like with few neutrophils and eosinophils. The patient did not respond to initial treatment with antihistamines, making urticaria less likely.

Tinea corporis is rare in neonates and can occur on any part of the body.[13] Morphologically, it can present as scaly annular lesions that are fixed and more persistent. Histologically, there are fungal hyphae and/or yeast in the stratum corneum with spongiotic dermatitis and parakeratosis. Our patient's lesions were not scaly, and the biopsy demonstrated minimal spongiosis. A periodic acid–Schiff special stain was negative for fungal microorganisms.

Neonatal lupus erythematosus can arise at birth or during the first few weeks of life.[16] Morphologically, the skin lesions occur on the scalp, forehead, or neck in a periorbital or malar distribution. They can present as erythematous, annular, scaly patches and plaques. Transplacental transmission of material autoantibodies has been implicated in the etiology, and a complication is infantile heart block. Histologically, a skin biopsy typically shows interface/lichenoid dermatitis. However, our patient's biopsy did not demonstrate interface changes, and serologically she was negative for autoantibodies.

Viral exanthems are skin eruptions that accompany underlying viral infections.[17] Morphologically, patients can present with an erythematous maculopapular rash, sometimes with vesicular, petechial, and urticarial lesions. Laboratory confirmation is made by virus-specific serologies. Histologically, viral exanthems can show a superficial, perivascular, lymphocytic infiltrate in the dermis, with reactive T cells and epidermal spongiosis. Our patient was afebrile and had no known sick contacts. A cytomegalovirus immunohistochemical study on the biopsy was negative, and an Epstein-Barr encoding region in situ hybridization study was negative.

Leukemia cutis is the infiltration of the skin by leukemic cells, most often in conjunction with systemic leukemia.[18] In infants and children, the most common leukemia is B-cell acute lymphoblastic leukemia. Morphologically, the skin lesions are characterized by single or multiple violaceous papules, nodules, and plaques. Histologically, there is a perivascular to interstitial infiltrate of atypical mononuclear cells in the dermis and sometimes subcutis. The leukemic cells demonstrate enlarged nuclei with coarse chromatin and prominent nucleoli. Increased mitotic activity may be seen with karyorrhectic debris. Immunohistochemically, the tumor cells can be positive for myeloperoxidase, CD43, CD68, CD34, and CD117.[18] Although our patient's biopsy demonstrated mononuclear cells with karyorrhexis, the cells did not have striking atypia and were negative for blast markers. A recent complete blood cell count on the patient was normal.

Conclusion

We report an unusual case of AEI with mononuclear cells consistent with helper T cells. One must keep these cells in mind when evaluating a biopsy of AEI, as they are benign and not suggestive of an atypical lymphoid infiltrate or leukemia cutis. This will prevent misdiagnosis and ensure that the patient receives appropriate management.

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APPENDIX

eTABLE. Summary of Annular Erythema of Infancy Cases

Reference (year)	Sex/age	Clinical description of rash	Anatomic location of rash	Duration of rash	Histopathology
Peterson and Jarratt[2] (1981)	M/6 mo	Intermittent urticarial eruption; some papules appeared to have enlarged centrifugally into 2–3-cm rings with urticarial borders	Generalized, sparing the palms and soles	8 mo	Moderate perivascular infiltrate of lymphocytes and eosinophils
Toonstra and de Wit[3] (1984)	F/8 mo	Large, irregularly shaped, annular lesions with red, raised, urticarial borders	Face, back, distal extremities	11 mo	Moderately dense perivascular infiltrates of lymphocytes, histiocytes, and numerous eosinophils present in the mid and lower dermis
Hebert and Esterly[4] (1986)	F/7 mo	Recurrent asymptomatic arcuate and annular skin lesions beginning as "little red dots" that enlarged rapidly into a palpable erythematous arc or ring	Shoulder, back, buttocks	14 mo	Mild acanthosis and a dense dermal perivascular infiltrate composed of lymphocytes, histiocytes, eosinophils, and a few plasma cells
Cox et al[5] (1987)	F/2 y	Asymptomatic annular plaques with wide, raised, firm, erythematous borders without vesiculation or formation of bullae	Generalized, face, upper trunk, feet	4 wk	Edematous dermis with an inflammatory infiltrate of lymphocytes, polymorphonuclear leukocytes, and histiocytes around blood vessels and to a lesser extent around nerves and sweat glands with no excess of eosinophils in the inflammatory infiltrate
Helm et al[6] (1993)	M/22 mo	Widespread erythematous eruption with no appreciable scale; lesions were annular and arciform with no vesicles, pustules, ulcers, or papules	Lower extremities	14 mo	Perivascular infiltrate with eosinophils
Kunz et al[7] (1998)	M/4 y	Nonitching erythematous papules on the trunk that evolved into annular and gyrate erythemas within weeks	Trunk	Several months	Striking eosinophilic inflammatory infiltrate predominantly in perivascular areas, without peripheral blood eosinophilia
Stachowitz et al[8] (2000)	M/4.5 mo	Well-demarcated, slightly itching, biocular erythema with a raised border	Periorbital regions	2.5 mo	NA
Wong et al[9] (2002)	F/15 y	Persisting extensive annular erythematous eruption since birth	Trunk	NA	Heavy mixed inflammatory infiltrate of lymphocytes, neutrophils, histiocytes, and eosinophils, both perivascularly and extending diffusely throughout the dermis

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eTABLE. (continued)

Reference (year)	Sex/age	Clinical description of rash	Anatomic location of rash	Duration of rash	Histopathology
Patrizi et al[10] (2008)	M/21 mo	Annular erythematous lesions with elevated borders and central resolution without scaling, vesicles, or crusts	Face, lower and upper extremities	NA	Diffuse interstitial and perivascular infiltrate of neutrophils and lymphocytes with nuclear dust
Saha et al[11] (2014)	M/5 d	Multiple brightly erythematous, annular plaques with palpable expanding borders and no detectable scaling or atrophy	Chest, back, arms, thighs, and face	NA	Superficial and deep perivascular lymphohistiocytic inflammatory infiltrate
Pfingstler et al[12] (2014)	F/5 d	Discrete, annular, erythematous plaques with raised borders and central clearing	Chest, arms, and neck	3–6 wk	Diffuse inflammatory infiltrate with a predominance of eosinophils
Del Puerto Troncoso et al[13] (2015)	F/2 y	Multiple annular and polycyclic, erythematous plaques with indurated borders and petechiae on the rims	Upper chest, abdomen, and upper back	NA	Superficial and deep perivascular and interstitial mixed-cell dermatitis, composed predominantly of neutrophils with abundant nuclear dust
Hamidi et al[14] (2018)	F/9 mo	Annular erythematous lesions with raised borders and central clearing	Face, arms, and legs	6 mo	Superficial and deep perivascular and interstitial infiltrate composed of numerous neutrophils and scattered eosinophils with nuclear dust
Patel et al[15] (2018)	Young child	Faint, nonscaling, annular, serpiginous, erythematous plaques with central clearing and barely elevated borders	Lower legs, abdomen, and buttocks	6 mo	Superficial and deep, perivascular, and interstitial inflammatory infiltrate consisting of lymphocytes, histiocytes, neutrophils, and eosinophils
Current case	F/11 mo	Annular erythematous patches and plaques	Back, arms, and legs	6 mo	Superficial to mid dermal, tight, coat sleeve–like, perivascular, lymphohistiocytic infiltrate admixed with rare neutrophils in eosinophils within the dermis

Abbreviations: M, male; F, female; NA, not available.