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Amitriptyline-induced erythema annulare centrifigum presenting as a pityriasiform eruption

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Abstract

Erythema Annulare Centrifugum (EAC) is an uncommon disease that presents as slowly-emerging, annular, erythematous lesions. Although the underlying etiology is often unknown, contributing factors such as infectious agents, pregnancy, underlying malignancy, and medications have all been implicated. We report a case of a 45-year-old woman with a pityriasiform eruption that persisted more than 6 months despite use of topical corticosteroids, oral antibiotics and oral antifungal agents. Clinical suspicion and repeat biopsy led to a diagnosis of amitriptyline-induced EAC. The patient was given a short course of prednisone and her amitriptyline was discontinued. Within three weeks the patient reported near complete resolution of her symptoms, which remained in remission at her six-month followup.

Keywords

Erythema annulare centrifugum; amitriptyline; pityriasis rosea; spongiosis

Abbreviations

EAC: Erythema annulare centrifugum; KOH: Potassium hydroxide; RPR: Rapid plasma regain; H&E: Hematoxylin and eosin

Background

Erythema Annulare Centrifugum (EAC) belongs to the heterogeneous group of gyrate erythemas first de-scribed by Darier in 1916 [1]. Typically, EAC starts as pink populous that enlarge over weeks to become an-nulare with trailing scale. The exact pathogenesis has not been identified but many triggers have been re-ported to induce EAC (Table 1). Our patient presented with EAC, and the clinical history and treatment re-sponse strongly suggested amitriptyline to be the culprit trigger.

Case Presentation

A 45-year-old woman with a past medical history of chronic headaches presented for evaluation of

a rash on her trunk (Figure 1). The rash started one month prior to presentation as a small patch on her abdomen which spread to other areas of her torso and proximal extremities. The lesions on her arms were mildly pruritic. Her medications included butabarbital 30 mg daily and amitriptyline 10 mg daily. Physical examination revealed small, scattered pink papules and plaques with occasional trailing scale (Figure 2). Potassium hydroxide (KOH) preparation showed an absence of hyphae. Rapid plasma reagin (RPR) testing was negative. The patient was treated with clocortolone cream. Pityriasis rosea was suspected, while EAC remained on the differential, although no source was identified. At her next visit five months later the eruption showed no improvement. A biopsy demonstrated spongiotic dermatitis, suggestive of pityriasis rosea or EAC. KOH examination of her feet demonstrated tinea pedis at this visit. The patient was given a 2 weeks steroid taper as well as terbinafine 250 mg daily for 2 weeks. Minimal improvement was noted at one month follow-up. A repeat biopsy displayed short mounds of parakeratosis surmounting narrow zones of spongiosis with superficial minimal inflammatory infiltrate of lymphocytes suggestive of EAC (Figures 3 & 4). Further medication review revealed that the patient started amitriptyline one month prior to onset of rash and thus the patient was diagnosed with amitryptiline-induced EAC. The patient was instructed to discontinue her amitriptyline and was given another 3-week prednisone taper. At six months follow-up, the patient reported complete resolution of her symptoms.

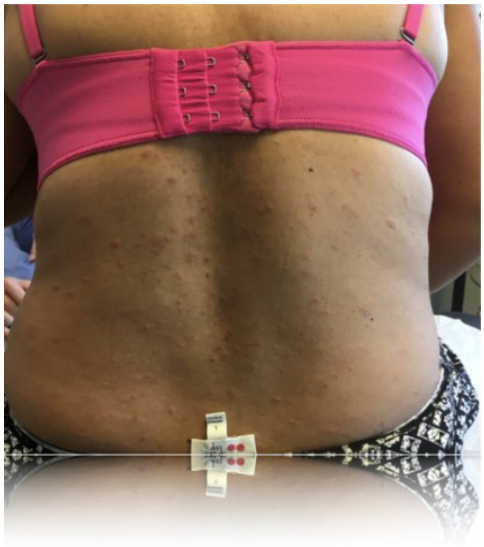

Figure 1: Scattered scaly erythematous papules and plaques on the lower back.

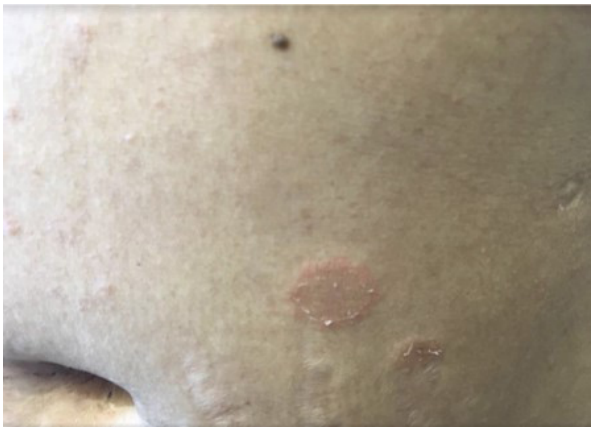

Figure 2: Close-up demonstrating circular erythematous plaques with trailing scale.

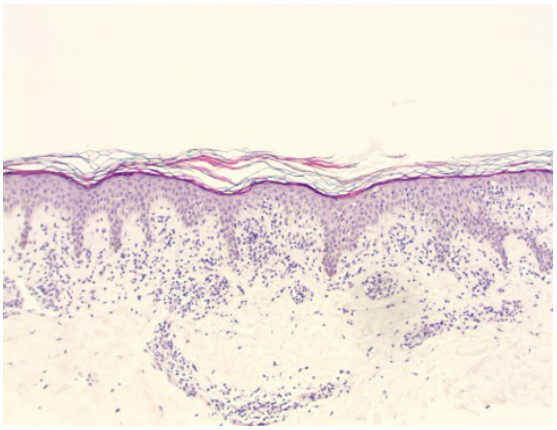

Figure 3: Short mounds of parakeratosis overlying mildly spongiotic epidermis and a superficial lymphohystiocytic infiltrate. H&E 10x.

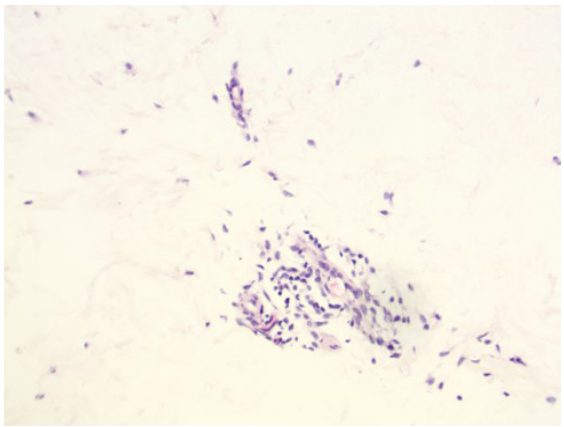

Figure 4: Perivascular lymphocytic infiltrate. H&E 40x.

Discussion

Erythema Annulare Centrifugum (EAC) belongs to the heterogenous group of gyrate erythemas first described by Darier in 1916 [1]. Although EAC has been noted in infants and elderly patients, it mostly commonly affects young and middle-aged adults and may possess a predilection for women [2,3]. The exact pathogenesis is unknown but it has been postulated to represent a hypersensitivity reaction to a myriad of reported triggers including infections, foods, medications, pregnancy, and malignancy (Table 1). EAC initially presents as a small, pink papule that gradually enlarges and develops a trailing scale over the course of weeks. In most cases the underlying cause is never identified.

Table 1: Reported causes and associations of erythema annular centrifugum

Category	Examples
Drugs	Aldactone, [4] progesterones, [5,6] ampicillin, [7] cimetidine, [8] amitriptyline [9]
Fungal	Superficial dermatophytes, [10] *Candida*, [11] Penicillium roqueforti via blue cheese ingestion [12]
Other infections	Molluscum virus, [13] tuberculosis, [14] Pediculosis pubis, [15] Epstein–Barr virus, [16] herpes zoster, [17] Coxiella burnetii, [18] recurrent appendicitis, [19] *E. coli* urinary tract infection, [20] *Ascaris* infection, [21] trypanosomiasis, [22] *Borrelia* spp. [23]
Endocrine	Hyperthyroidism, [24] Hashimoto's thyroiditis, [25] autoimmune progesterone dermatitis,[26] pregnancy,[27-29] polyglandular autoimmune syndrome type I (the latter possibly mediated by *Candida* infection) [30]
Immunologic	Sarcoidosis, [31] autoimmune hepatitis, [32] autoimmune pancreatitis, [33] relapsing polychondritis, [34] Crohn's disease, [35] bullous pemphigoid, [36] Sjogren's[3] [37,38] linear IgA dermatosis [39,40]
Hematologic	Anaplastic large cell lymphoma, [41] chronic myelogenous leukemia, [42] chronic lymphocytic leukemia, [43,44] and thrombocythemia [45]
Other neoplastic	Carcinomas of the prostate,[46] stomach, [47] nasopharynx, [48] breast, [49] ovary, [50] squamous cell lung carcinoma, [51] carcinoid tumor, [52] mycosis fungoides, [53]
Miscellaneous	Annually recurring EAC, [54] familial, [55,56] infantile-onset, [57] post surgery [58]

Decades after Darier initially described it, Ackerman further classified EAC into superficial and deep vari-ants [59]. These variants are distinct enough for some to suggest they are not the same disease [60]; indeed, Ackerman devised the terms superficial gyrate erythema and deep gyrate erythema to help delineate the two.

The superficial variant presents clinically with superficial scaling at the trailing edge of the lesion. Histo-logic examination reveals superficial perivascular lymphocytic infiltrate (Figure 4) with occasional histio-cytes and, rarely, eosinophils. The papillary dermis will be slightly edematous. Some focal spongiosis and parakeratosis are common as well.

The lesions first coined by Darier as EAC are what we now classify as the deep variant of EAC. These le-sions exhibit a red, recurrent, annular pattern with firm, cordlike borders. They are devoid of scale and typi-cally are non-pruritic. The histological features are similar to superficial EAC, but the characteristic "coat-sleeve" perivascular infiltrate primarily affects the dermis, leaving the epidermis largely unaffected. Some have suggested that the deep variant of EAC may actually be an annular form of tumid lupus erythemato-sus due to the striking resemblance shared by the two disease processes [61].

In patients of advanced age or with relevant medical history, an investigation into possible neoplastic caus-es is reasonable, but not recommended in the absence of other clues. In our patient's case, she was fortunate to have a previously described trigger, amitriptyline,62 that could be easily discontinued and lead to resolu-tion of her symptoms. Numerous empirical treatments have been identified as successful in the literature. They include vitamin D analogues, [63] narrow band UVB therapy, [64] allergen avoidance, [65] cyclospor-ine, [66] dapsone, [67] nicotinamide, [68] antifungals for causative superficial dermatophyte infections, [69] and various antimicrobials such as metronidazole [70] and sulfonamides [71]. Our patient's rapid recovery with cessation of amitriptyline suggest strongly that the drug was the culprit in her development of EAC.

Conclusion

Erythema annulare centrifugum is a condition with a potentially chronic, relapsing and remitting course that has a wide range of triggers and varied response to treatment. It can mimic other common entities such as tinea corporis or pityriasis rosea and should be on the differential when standard therapies fail to treat a slowly enlarging, erythematous, annular rash with trailing scale. Identification of erythema annular cen-trifugum is also important as it may prompt workup to identify an underlying causative malignancy.

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