

Metformin Induced Erythema Annulare Centrifugum Mimicking Community Acquired MRSA Skin Infections

Garrastegui-Mercado, Emmanuel, MD, Antony, Suresh, MD

Background

- Erythema annulare centrifugum (EAC), first described by Darier, is an adverse effect that can be associated with drugs, infection, autoimmune or neoplastic disease. However, most cases of EAC remain unexplained.
- We report a case of EAC induced by metformin that was treated with antibiotics for several months before the clinical diagnosis was made. A 59 year-old male with diabetes on metformin who presented with multiple hyperpigmented lesions which were non painful and urticarial over the legs and arms (Images, Group A).
- Patient was previously treated as a community acquired MRSA(CA-MRSA) skin infection with several courses of antibiotics with no response. Skin biopsy demonstrated acanthosis, focal parakeratosis, mild spongiosis and pattern of inflammation suggestive of EAC.
- This case presents an opportunity to discuss the unusual adverse effects of metformin that could mimic common skin infections seen in clinical practice.

Objective

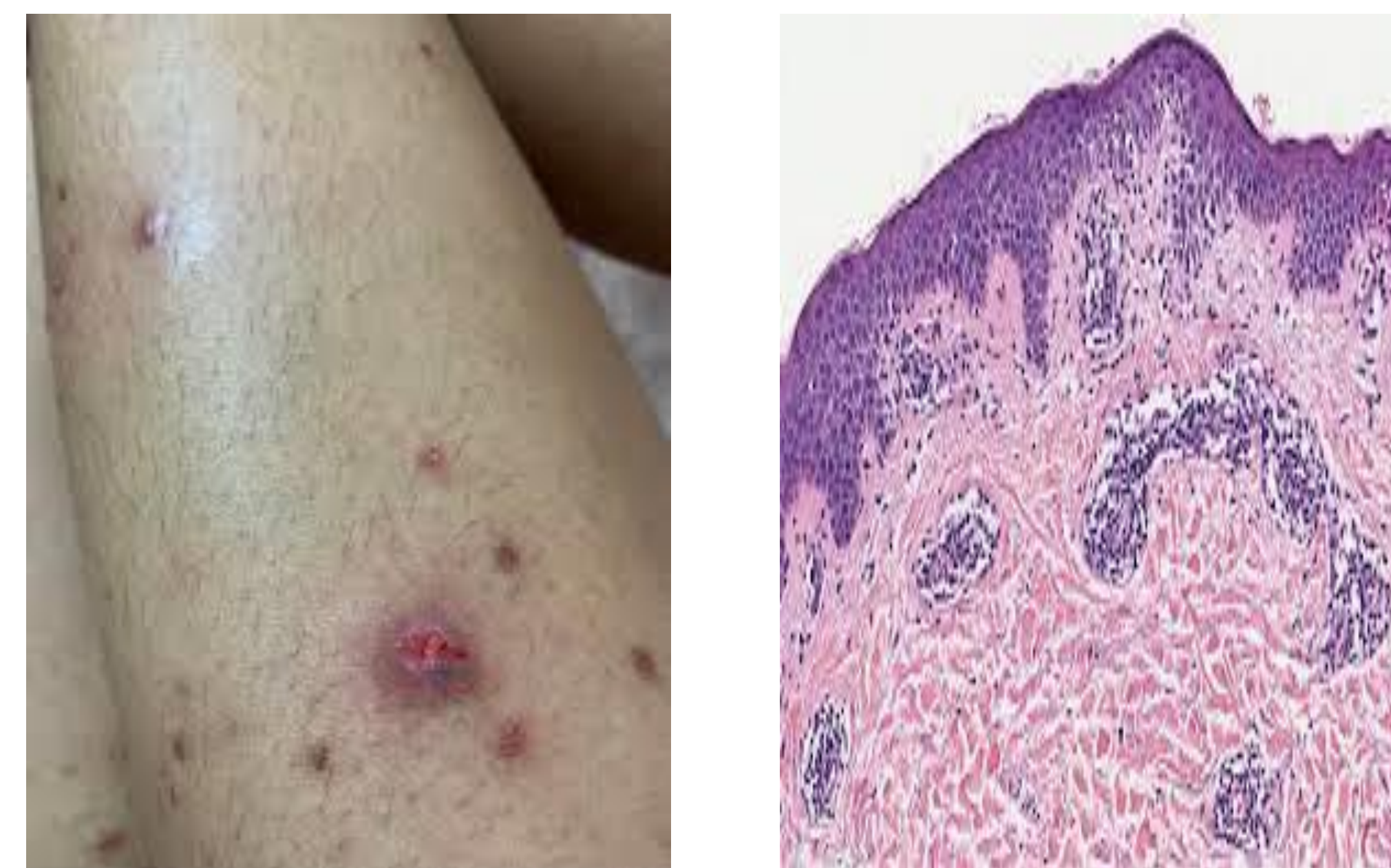
CA-MRSA skin infections have been well documented, however metformin induced adverse effects can rarely mimic these skin infections. We present a rare case of EAC induced by metformin that clinically mimicked CA-MRSA. Here we discuss the potential impact of missed diagnosis of metformin induced skin lesions that are being treated as bacterial skin infections.

Images



Group A: Patient hyperpigmented lesions in upper and lower extremities

Images



Group B: Examples of CA-MRSA skin lesions and histologic appearance of EAC, respectively.

Results

Citation	Pathophysiology	Metformin induced skin reactions
Pierre Fabre Group, 2012	Transitory inhibition of the hair cycle	Alopecia
Pierre Fabre Group, 2013	Urticaria-like reaction	Angioedema
Pierre Fabre Group, 2018	Poorly understood	Buccal Lichen planus
Voore et al, 2016	Type IV Hypersensitivity Reaction	DRESS Syndrome
Pierre Fabre Group, 2012	Type IV Hypersensitivity reaction	Eczematous Dermatitis
Pierre Fabre Group, 2010; Steber et al, 2016; Beliver et al, 2017	CD8 lymphocytes mediated cytotoxicity	Fixed pigmented erythema
Pierre Fabre Group, 2012	Pharmacological mediated	Flush
Salem et al, 2006	Immune response to precipitating antigen	Leukocytoclastic vasculitis
Pierre Fabre Group, 2012	Cytotoxicity mediated immune response to antigen(drug) attached to epidermal lining	Lichenoid eruption
Pierre Fabre Group, 2019	Lymphocytes mediated immune reaction	Maculopapular exanthema
Pierre Fabre Group, 2012	Multiple mechanisms involved	O edema
Pierre Fabre Group, 2012	Autoimmune response to epidermis specific antigens	Pemphigus
Pierre Fabre Group, 2018	Multiple mechanisms involved	Peripheral edema
Pierre Fabre Group, 2012	Variable	Photosensitivity
Pierre Fabre Group, 2019; Harris et al, 1971	Reactive oxygen species mediated photosensitivity reaction	Photosensitization
Pierre Fabre Group, 2012	Multiple mechanisms involved, autoimmune and non-autoimmune mediated reactions	Pruritus
Pierre Fabre Group, 2012	Phototoxicity	Pseudoporphyria
Pierre Fabre Group, 2012	Thrombocytopenia	Purpura
Pierre Fabre Group, 2012	Impaired external thermoregulation	Rosacea
Mumoli et al, 2014	Possible type 1 Hypersensitivity reaction	Rosacea-like facial Rash
Pierre Fabre Group, 2012	Multiple mechanisms involved, autoimmune and non-autoimmune mediated reactions	Urticaria

Discussion

- First described by Darier in 1916, Erythema annulare centrifugum (EAC) is an annular, erythematous lesion that appears as urticarial-like papules and enlarges centrifugally, then clears centrally (2). Has been associated with various underlying conditions, including drugs reactions. EAC appears to be an uncommon disorder; however, the prevalence and incidence are unknown. Is often described in adults but may also occur in children.
- EAC had been related to multiple drugs, among them the antidiabetic drug Metformin. A list of the known drug-induced skin reactions to metformin are presented in Table 1 (1). The pathogenesis of EAC is unclear but is thought to be a delayed-type hypersensitivity response to a wide variety of antigens.
- Cutaneous drug reactions are a challenging diagnostic problem since they can mimic a large variety of skin diseases including bacterial skin infections like CA-MRSA skin lesions (Image A, Group B)(3). EAC can be diagnosed based upon recognition of the classic clinical presentation but a skin biopsy should be performed to exclude alternate diagnoses. Histopathologic findings in EAC can exhibit a dense, perivascular, lymphocytic, inflammatory along with possible alterations in the papillary dermis and epidermis, including edema, spongiosis, parakeratosis, hyperkeratosis, and basal layer vacuolization (Image B, Group B)(4).
- Data on the treatment of EAC is limited, and there is no effective therapy. Clinical experience suggests that EAC can improve upon treatment of an associated underlying disease or removal of an associated exposure (5). Topical or intralesional corticosteroids, antipruritic agents and some oral antimicrobial drugs have been reported to improve EAC in small numbers. EAC may wax and wane over months to years, but most cases eventually resolve spontaneously (4).

Conclusion

In conclusion, EAC is a benign annular erythematous eruption that presents as a cutaneous hypersensitivity reaction to multiple causes. EAC is thought to be highly associated with adverse drug reactions, but it may be very difficult to prove a causal relationship. We recommend that skin biopsy is the mainstay of the diagnosis of EAC. EAC should be included in the differential diagnosis of unusual skin lesions in the appropriate setting.

References

1. EMJ Dermatol. 2020;8[1]:50-53. Abstract Review No. AR5.
2. McDaniel B, Cook C. Erythema Annulare Centrifugum. [Updated 2021 Aug 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482494/>
3. Nigen S, Knowles SR, Shear NH. Drug eruptions: approaching the diagnosis of drug-induced skin diseases. J Drugs Dermatol. 2003 Jun;2(3):278-99. PMID: 12848112.
4. Kim KJ, Chang SE, Choi JH, Sung KJ, Moon KG, Koh JK. Clinicopathologic analysis of 66 cases of erythema annulare centrifugum. J Dermatol. 2002 Feb;29(2):61-7. doi: 10.1111/j.1346-8138.2002.tb00167.x. PMID: 11890297.
5. Meena D, Chauhan P, Hazarika N, Kansal NK, Gupta A. Aceclofenac-Induced Erythema Annulare Centrifugum. Indian J Dermatol. 2018 Jan-Feb;63(1):70-72. doi: 10.4103/ijd.IJD_728_16. PMID: 29527030; PMCID: PMC5838759.