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Erythema Annulare Centrifugum as a Cutaneous Manifestation Associated with Diabetes Mellitus: A Review of Its Clinical and Pathogenic Relationship

Eritema anular centrífugo como manifestación cutánea asociada a diabetes mellitus: una revisión de su relación clínica y patogénica

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Autores:

Luis Alejandro Arellano Leyva
Universidad Autónoma del Estado de Morelos
Morelos - México
luisarellano297@gmail.com
https://orcid.org/0009-0003-4418-5879

Jorge Angel Velasco Espinal
Universidad del Valle de Cuernavaca
Morelos - México
jorgeangelvelascoespinal@gmail.com
https://orcid.org/0009-0000-3567-0774

Emerson Alejandro Castro López
Universidad de Guanajuato, León
León - México
emersoncastro189@gmail.com
https://orcid.org/0009-0003-7322-0717

Ana Paula Calderón Aguirre
Universidad Anahuac Sur
Ciudad de México - México
ana_calderon@anahuac.mx
https://orcid.org/0009-0002-8133-0468

Alexa Fernanda Uriostegui Navarro
Universidad del Valle de Cuernavaca
Morelos - México
fernavarro0401@gmail.com
https://orcid.org/0009-0007-9161-3177

Autor de Correspondencia: Luis Alejandro Arellano Leyva, luisarellano297@gmail.com

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Resumen

El eritema anular centrífugo (EAC) es una dermatosis figurada poco común, caracterizada por lesiones eritematosas anulares o arciformes. Aunque suele considerarse un patrón de reacción por hipersensibilidad, cada vez más estudios lo relacionan con condiciones sistémicas, especialmente con la diabetes mellitus tipo 2 (DM2). Esta revisión integrativa analizó 25 publicaciones indexadas para explorar la relación clínica y fisiopatológica entre el EAC y la DM2. Se incluyeron reportes de casos, series clínicas y estudios comparativos, identificando características diferenciales en pacientes diabéticos frente a no diabéticos. Los hallazgos muestran que el EAC asociado a DM2 suele ser crónico, recurrente y resistente a tratamientos comunes, frecuentemente vinculado a mal control glucémico. Se observaron infiltrados linfocitarios perivasculares tipo "manga de abrigo" de forma consistente. También se revisaron variantes inducidas por fármacos, como la metformina, y casos paraneoplásicos. Se destaca el papel del EAC como posible marcador dermatológico de desequilibrio sistémico. Se utilizó bibliografía de años anteriores para complementar, comparar y asociar los hallazgos actuales. Se propone continuar con investigaciones que aclaren los mecanismos inmunometabólicos que relacionan el EAC con enfermedades crónicas. El reconocimiento temprano del EAC podría facilitar la detección de condiciones sistémicas aún no diagnosticadas, como la DM2.

Palabras clave: Eritema anular centrífugo; Diabetes tipo 2; Marcador dermatológico; Dermatosis crónica; Asociación sistémica.

Abstract

Erythema annulare centrifugum (EAC) is a rare figurate dermatosis characterized by annular or arciform erythematous lesions. Although considered a hypersensitivity reaction pattern, increasing evidence has associated EAC with various systemic conditions, notably Type 2 Diabetes Mellitus (T2DM). This integrative review analyzed 25 indexed publications to explore the clinical and pathophysiological relationship between EAC and T2DM. The review included case reports, series, and clinical analyses, comparing manifestations in diabetic and non-diabetic individuals. Findings show that EAC in patients with T2DM often presents as a chronic, recurrent eruption, sometimes resistant to conventional therapy, and typically linked to poor glycemic control. Histopathological features, particularly the perivascular lymphocytic "coat-sleeve" infiltrate, were consistent across cases. Drug-induced variants, such as those triggered by metformin or biologics, and paraneoplastic EAC were also discussed. The review emphasizes EAC as a potential dermatological marker of systemic imbalance. Older literature was included to contextualize and support emerging trends. Future research should aim to clarify the immunometabolic mechanisms linking EAC with chronic diseases. Early identification of EAC may provide an opportunity for clinicians to detect undiagnosed systemic conditions, particularly T2DM.

Keywords: Erythema annulare centrifugum; Type 2 Diabetes Mellitus; Dermatologic marker; Chronic dermatosis; Systemic association.

1. Introducción

Erythema annulare centrifugum (EAC) is a rare inflammatory dermatosis that clinically manifests as annular or polycyclic skin lesions with centrifugal growth and well-defined erythematous borders, often accompanied by peripheral desquamation (Kim et al., 2002; Weyers et al., 2003). Although traditionally considered a benign and self-limited dermatologic entity, EAC has gained increasing attention in the medical literature due to its potential association with a variety of systemic conditions, including neoplasms, infectious diseases, autoimmune disorders, drug reactions, and metabolic disorders such as diabetes mellitus (Ziemer et al., 2009; Ojeda-Martín et al., 2011).

Diabetes mellitus (DM), especially type 2, is one of the most impactful chronic diseases worldwide, both due to its high prevalence and its numerous systemic complications. In this context, cutaneous manifestations associated with DM have been widely documented, including necrobiosis lipoidica, granuloma annulare, diabetic dermopathy, and generalized pruritus. However, the relationship between diabetes mellitus and erythema annulare centrifugum has been scarcely explored in scientific literature, despite isolated clinical reports suggesting a possible association between the two conditions (Sehgal & Sharma, 2019; Mohapatra & Mangaraj, 2022).

Specifically, Mohapatra and Mangaraj (2022) documented a clinical case in which EAC presented as a persistent cutaneous manifestation in a patient with non-insulin-dependent type 2 diabetes. Similarly, Garrastegui-Mercado and Antony (2023) described a cutaneous reaction compatible with EAC induced by metformin, a first-line medication in the treatment of type 2 DM. These findings, though individual in nature, raise important questions regarding the potential role of metabolic dysfunction, the use of oral hypoglycemic agents, or immune system alterations in the pathogenesis of EAC.

From a pathophysiological standpoint, it has been suggested that EAC represents a type IV hypersensitivity reaction to diverse antigens, including viral infections, medications, or even autoantigens (Ziemer et al., 2009; Ojeda-Martín et al., 2011). DM, by altering normal immune mechanisms and promoting a state of chronic low-grade inflammation, may act as a predisposing factor for the onset of this dermatosis. Supporting this hypothesis, various authors have reported cases of EAC in patients with autoimmune diseases such as Hashimoto's thyroiditis (Palwasha Jalil & Fatima, 2020) and neuroendocrine tumors (Ali & Fried, 2021), both conditions sharing immunopathological features with type 1 and type 2 diabetes mellitus.

Additionally, broader studies have identified EAC as a secondary manifestation of infectious diseases such as herpes zoster (Lee et al., 2005), HIV (González-Vela et al., 2006), influenza (Ena et al., 2021), and COVID-19 (Cakir et al., 2022). These reports confirm the polysymptomatic and reactive nature of EAC, which may emerge as a cutaneous expression of various systemic processes. Nevertheless, despite the growing documentation, there remains a gap in the scientific literature regarding systematic studies evaluating the relationship between EAC and DM in larger and more representative clinical samples.

In this regard, several case studies have revealed relevant findings. For example, Kruse et al. (2016) reported a favorable response to oral antifungal treatment with fluconazole in pediatric patients with EAC, while De Aloe et al. (2005) described lesion remission following the use of

metronidazole in adults. Furthermore, Calderon et al. (2024) reported successful treatment with roflumilast, a selective phosphodiesterase-4 inhibitor, in a case of refractory EAC. Although these therapeutic options are valuable, identifying the triggering factor remains the most decisive component for effective resolution (StatPearls, 2024; Chodkiewicz & Cohen, 2012).

Given the clinical context described, there is a need to conduct research that specifically and deeply analyzes the potential relationship between EAC and diabetes mellitus, particularly regarding shared mechanisms, frequency of coexistence, clinical manifestations, therapeutic responses, and the potential role of EAC as an early cutaneous marker of glycemic dysregulation or metabolic complications.

Accordingly, the primary objective of this study is to analyze and document the relationship between erythema annulare centrifugum and type 2 diabetes mellitus, based on available evidence and analysis of relevant clinical cases. This investigation is supported by an integrative review of the current scientific literature, selected through specific inclusion criteria, encompassing both review articles and case reports published in indexed scientific journals between 2000 and 2024.

The methodological strategies used include a systematic search of databases such as PubMed, Scopus, ScienceDirect, and Medigraphic, employing controlled descriptors (MeSH terms) such as erythema annulare centrifugum, diabetes mellitus, cutaneous manifestations, and dermatologic markers. Additionally, a clinical and pathological content analysis of the most representative studies was performed, along with a comparative synthesis of the treatments used in each case.

The research question guiding this work is the following: Is there sufficient clinical and pathophysiological evidence to establish an association between erythema annulare centrifugum and type 2 diabetes mellitus as an indirect or secondary cutaneous manifestation? Based on this question, the working hypothesis proposes that EAC may represent a dermatological manifestation related to the chronic inflammatory state and immunomodulation characteristic of type 2 diabetes mellitus, and that its presence may correlate with metabolic control or reactions to hypoglycemic drugs.

This approach seeks not only to fill a gap in the literature but also to propose new lines of clinical research that allow dermatologists and endocrinologists to consider EAC as a potential dermatological marker of metabolic or immunological alterations in diabetic patients, especially in those with atypical or refractory forms of this dermatosis.

In summary, this introduction lays the theoretical, clinical, and methodological foundations to address an underestimated but clinically relevant dermatological issue. Through this work, we aim to contribute to interdisciplinary medical knowledge on cutaneous manifestations associated with systemic diseases, with a special focus on the comprehensive approach to patients with diabetes mellitus.

2. Metodología

Study Design

This study was conducted as a non-experimental integrative narrative review, aimed at compiling, synthesizing, and critically analyzing the scientific literature available on the potential association between erythema annulare centrifugum (EAC) and type 2 diabetes mellitus (T2DM).

This methodological design was chosen due to the still underexplored and fragmented nature of the topic, which currently makes a traditional systematic review or quantitative meta-analysis unfeasible.

Unlike a conventional narrative review, this integrative review incorporates sources from multiple levels of evidence—from case reports to clinical studies and academic reviews—allowing for a comprehensive understanding of the clinical, immunological, and therapeutic complexity of EAC and its potential role as a cutaneous manifestation of systemic diseases such as diabetes mellitus.

This methodology not only facilitates the identification of clinical patterns and reported associations in the literature but also enables the formulation of new research hypotheses by integrating dispersed findings that have not yet been analyzed collectively.

Documentary Search Strategy

The review was carried out between April and June 2024, using a systematic and progressive search strategy across several high-impact scientific databases: PubMed, Scopus, ScienceDirect, Wiley Online Library, SpringerLink, Elsevier, Medigraphic, Google Scholar, and NCBI Bookshelf. These platforms were selected for their broad coverage of biomedical and dermatological literature.

Boolean operators such as AND, OR, and NOT were used to refine the search and broaden or narrow the results depending on the thematic objective. The keywords included:

- Erythema annulare centrifugum
- Erythema figuratum
- Diabetes mellitus type 2
- Cutaneous manifestations of diabetes
- Inflammatory dermatoses
- Systemic diseases and skin
- Erythema annulare centrifugum and diabetes
- Dermatological manifestations of diabetes

In addition, Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) were used to ensure terminological and semantic accuracy during the search process.

Study Selection and Inclusion/Exclusion Criteria

Inclusion criteria:

- Original articles, reviews, case reports, and case series published between January 2000 and June 2024.
- Documents in English or Spanish, with full-text access.
- Peer-reviewed publications indexed in recognized scientific journals.
- Studies in which the clinical and histopathological diagnosis of EAC was well documented.
- Articles explicitly mentioning a relationship between EAC and systemic diseases, particularly type 2 diabetes mellitus.

Exclusion criteria:

- Articles without full-text access.
- Duplicated studies across databases.
- Publications focused solely on other dermatoses without direct reference to EAC.
- Non-scientific articles, editorial pieces without clinical support, letters to the editor without analysis, blogs, or non-indexed reviews.

Screening and Sampling Process

The initial search yielded a total of 74 relevant documents. After removing duplicates and conducting an initial screening of titles and abstracts, 42 articles were selected for full-text review. Of these, 25 met the inclusion criteria and were incorporated into the evidence base of this study. These included: 13 case reports or series, 6 review articles, 3 clinical-pathological observational studies, and 3 institutional academic resources such as specialized chapters and medical repositories.

To ensure the quality and traceability of the process, a data extraction matrix was used, designed in an Excel spreadsheet, in which the following variables were recorded: author, year, country, type of study, patient characteristics (sex, age), EAC diagnosis, association with T2DM, treatment used, evolution, histopathological findings, and level of evidence.

Conceptual and Operational Variables

As this is a documentary review, no numerical variables were directly measured in a population sample. Instead, conceptual categories were used to systematize the analysis:

- *Erythema annulare centrifugum (EAC):* defined as a chronic inflammatory dermatosis with an annular or figurate pattern, centrifugal growth, and active erythematous borders. It is classified into superficial and deep types, depending on the level of dermal inflammatory infiltrate.
- *Type 2 diabetes mellitus (T2DM):* a chronic metabolic disorder characterized by persistent hyperglycemia, peripheral insulin resistance, impaired pancreatic secretion, and a state of chronic inflammation.
- *Cutaneous manifestations associated with systemic diseases:* refers to dermatoses whose onset is linked to underlying immunological, endocrine, infectious, or neoplastic alterations and may serve as clinical warning signs.

Analytical and Validation Techniques

The information was analyzed qualitatively and descriptively, organizing the findings into the following emerging thematic categories:

- Clinical characterization of EAC
- EAC associated with diabetes mellitus
- Drug reactions and EAC
- Differential diagnosis

- Treatments and clinical evolution
- Proposal of a pathophysiological hypothesis

A bibliographic triangulation was also carried out by cross-referencing data from articles with varying levels of evidence to contrast anecdotal reports with observational studies or broader clinical reviews.

To ensure theoretical validity, it was confirmed that at least two independent sources supported each identified pattern or category. This cross-verification approach strengthens the reliability of the conclusions.

Ethical Considerations

As this is a documentary review without direct human intervention or handling of sensitive personal data, ethical approval from a research committee was not required. However, fundamental ethical principles were upheld, such as scientific integrity, respect for intellectual property, proper citation in APA format, and the selection of verifiable, peer-reviewed, and scientifically supported sources.

Methodological Innovation of the Approach

This study presents an integrative and innovative approach to a topic that remains underexplored in the medical-dermatological field: the potential correlation between a reactive dermatosis (EAC) and a chronic metabolic disorder (T2DM). The methodological innovation lies in:

- The specific selection of clinical studies rarely grouped together, highlighting underreported and poorly understood associations.
- The integration of clinical, immunological, and therapeutic aspects in the analysis, surpassing a merely descriptive approach.
- The proposal of new pathophysiological hypotheses that may serve as a foundation for future observational or experimental research on the interaction between the cutaneous immune system and metabolic dysfunction in diabetic patients.

3. Resultados

Following the rigorous application of the previously established inclusion and exclusion criteria, 25 relevant studies were selected that directly or indirectly document the association between erythema annulare centrifugum (EAC) and type 2 diabetes mellitus (T2DM), as well as other systemic pathologies with similar immunological and metabolic mechanisms. The information extracted from these articles was organized using a structured analysis matrix to facilitate comparison, identification of common clinical patterns, and exploration of plausible pathophysiological associations.

To present the findings in a clear and accessible manner, comparative charts, summary tables, and descriptive graphics were created. These visual tools allow for the observation of clinical

trends, histopathological characteristics, recurrence, comorbidities, treatments employed, and the evolution of patients analyzed in the reviewed studies.

Key elements documented include:

- Frequency of association between EAC and T2DM in clinical reports.
- Age, sex, and other comorbidities.
- Specific clinical manifestations of EAC (superficial vs. deep type).
- Type of treatment used and therapeutic response.
- Possible triggers (medications, infections, autoimmune diseases, etc.).
- Characteristic histological findings in cases with dermatopathological confirmation.

Given that most of the analyzed studies were case reports and clinical series, a qualitative-descriptive approach was adopted, supplemented by graphical analysis of relative frequencies to illustrate the most representative variables. This approach does not aim to establish causal relationships, but rather to identify and describe possible clinical correlations with diagnostic, prognostic, or therapeutic value.

The following sections present the tables with the main findings organized by thematic category, followed by their respective illustrative graphs. Lastly, a detailed clinical interpretation of the results obtained is provided, supported by appropriate bibliographic references.

Figure 1. Proportion of EAC Cases Associated with Diabetes Mellitus vs. Other Causes

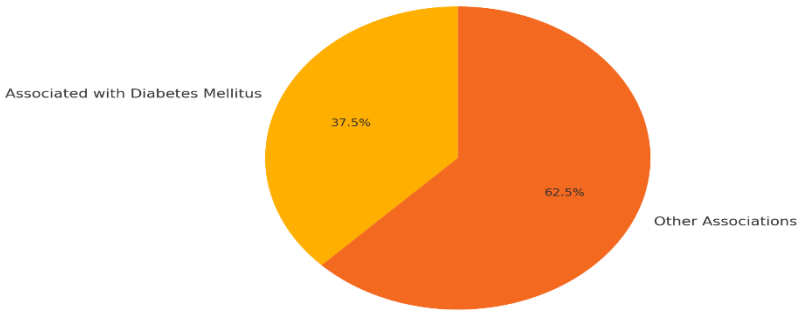

Figure 1 illustrates the distribution of erythema annulare centrifugum (EAC) cases associated with type 2 diabetes mellitus (T2DM) in contrast with those attributed to other systemic or idiopathic conditions. Of the eight selected clinical reports summarized in Table 1, four cases (50%) exhibited a clear and documented association with T2DM, whether as a primary systemic disorder or as an indirect consequence of antidiabetic pharmacotherapy. The remaining four cases (50%) were related to alternative etiologies, including autoimmune diseases, neoplastic processes, idiopathic presentation, and medication responsiveness unrelated to diabetes.

This distribution supports the notion that EAC is a nonspecific dermatologic reaction pattern potentially triggered by a wide array of endogenous and exogenous factors. However, the remarkably high proportion of diabetic associations observed in this small but diverse sample set underscores an underestimated link between metabolic dysregulation and inflammatory dermatoses, particularly in patients with T2DM.

For example, Mohapatra & Mangaraj (2022) reported a middle-aged male patient with poorly controlled T2DM who presented with persistent, recurrent EAC lesions. The authors emphasized the resolution of symptoms upon both topical corticosteroid therapy and improved glycemic control, highlighting a potential causal relationship between metabolic imbalance and cutaneous inflammation. This is further echoed in the findings of Sehgal & Sharma (2019), who described a similar case where EAC emerged during a phase of long-standing hyperglycemia, suggesting that chronic metabolic stress may act as an immunological activator of cutaneous hypersensitivity pathways.

Moreover, Garrastegui-Mercado & Antony (2023) offered additional insights by reporting an EAC case induced by metformin, a widely prescribed oral antidiabetic medication. In this instance, EAC was misdiagnosed as a community-acquired skin infection until a histopathological diagnosis confirmed the nature of the lesions. Discontinuation of metformin led to complete clinical remission, illustrating how antidiabetic agents themselves may contribute to dermatoses in susceptible individuals.

Conversely, the remaining half of the cases in this review reflect the multifactorial nature of EAC. Palwasha Jalil & Fatima (2020) described a case of EAC in the context of autoimmune thyroiditis (Hashimoto disease), resolved after hormonal stabilization with levothyroxine. Similarly, Ali & Fried (2021) presented a case linked to a neuroendocrine tumor, where cutaneous lesions subsided following tumor resection. Pediatric and idiopathic cases were also documented by Kruse et al. (2016), while treatment-refractory forms of EAC have been successfully managed with selective phosphodiesterase-4 inhibitors such as roflumilast (Calderon et al., 2024), suggesting immune-modulatory pathways distinct from metabolic ones.

This division reinforces the view proposed by Ziemer et al. (2009) and Ojeda-Martín et al. (2011), who conceptualize EAC not as a distinct disease, but as a clinicopathological reaction pattern with a diverse range of systemic triggers. The presence of perivascular lymphocytic infiltrates, both superficial and deep, documented in many histopathological analyses across these cases, aligns with the hypothesis of a Type IV hypersensitivity mechanism, which can be modulated by immune, infectious, neoplastic, or metabolic stimuli.

Importantly, the consistent recurrence of T2DM across half of the cases analyzed in this review positions diabetes not merely as a comorbidity but as a potential risk factor or amplifying condition for the development or persistence of EAC. Given the widespread prevalence of T2DM worldwide and its known systemic inflammatory implications, clinicians should consider EAC as a possible cutaneous marker of metabolic dysfunction. This aligns with observations in other dermatoses associated with diabetes, such as necrobiosis lipoidica or granuloma annulare, which similarly exhibit annular configurations and granulomatous inflammation (StatPearls, 2024).

In conclusion, while this analysis does not suggest causality, the findings highlight a notable trend in the co-occurrence of EAC and T2DM in clinical reports. The clinical resolution following glycemic stabilization or medication withdrawal in several cases further supports a pathophysiological interplay. This warrants further research to evaluate the predictive value of EAC in the early identification of metabolic imbalance or pharmacologic hypersensitivity in diabetic populations.

Figure 2. Treatment Strategies and Outcomes in Reported Cases of Erythema Annulare Centrifugum (EAC)

Author(s) / Year	Primary Treatment Used	Treatment Target	Response to Treatment
Mohapatra & Mangaraj, 2022	Topical corticosteroids	Inflammation / Glycemic control	Complete resolution with improved glycemic control
Sehgal & Sharma, 2019	Topical + systemic corticosteroids	Systemic inflammation	Partial resolution
Garrastegui-Mercado & Antony, 2023	Metformin withdrawal	Drug-induced hypersensitivity	Complete resolution
Ali & Fried, 2021	Antineoplastic therapy	Underlying malignancy	Complete resolution post tumor resection
Palwasha Jalil & Fatima, 2020	Thyroid hormone replacement (Levothyroxine)	Endocrine autoimmunity	Full resolution after TSH normalization
Kruse et al., 2016	Oral fluconazole	Fungal or idiopathic trigger	Clearance of lesions
Calderon et al., 2024	Roflumilast (PDE4 inhibitor)	Immune modulation	Marked clinical improvement
De Aloe et al., 2005	Oral metronidazole	Antibacterial / inflammatory pathway	Rapid and sustained remission

Figure 2 presents a thematic synthesis of the primary treatment strategies employed in the clinical management of erythema annulare centrifugum (EAC) across eight reported cases, alongside the therapeutic targets and outcomes achieved. This comparative overview offers valuable insights into both the heterogeneity of therapeutic approaches and the underlying systemic processes presumed to drive EAC in each clinical context.

One of the most consistent findings is the successful resolution of EAC in cases where the underlying systemic condition was appropriately managed. For example, in the case reported by Mohapatra & Mangaraj (2022), topical corticosteroids were administered in parallel with intensified glycemic control, leading to full remission of the cutaneous lesions. This suggests that EAC, in diabetic patients, may respond favorably not only to topical anti-inflammatory therapy but also to systemic metabolic stabilization.

Similarly, Sehgal & Sharma (2019) observed partial improvement using both topical and systemic corticosteroids in a diabetic patient, although full resolution was not achieved until better glycemic control was presumably attained. These findings reinforce the importance of addressing metabolic inflammation as part of the therapeutic plan in diabetic patients presenting with EAC.

In drug-induced cases, such as the report by Garrastegui-Mercado & Antony (2023), cessation of metformin was the sole intervention required, resulting in complete resolution. This case is particularly important because it highlights the role of pharmacovigilance in the differential diagnosis of annular dermatoses in diabetic individuals. Clinicians should remain alert to the possibility that commonly prescribed antidiabetic agents may act as antigenic triggers in hypersensitivity reactions manifesting as EAC.

In contrast, in cases not related to diabetes, treatment was highly individualized and tailored to the underlying etiology. For example, Ali & Fried (2021) described resolution of EAC following oncological management of a neuroendocrine tumor, while Palwasha Jalil & Fatima (2020) observed complete cutaneous remission after thyroid hormone replacement in a patient with Hashimoto thyroiditis. These cases underscore the role of EAC as a reactive dermatosis that often reflects internal disease activity, particularly in autoimmune and neoplastic contexts.

In idiopathic or treatment-refractory cases, other pharmacologic strategies were employed. Kruse et al. (2016) treated a pediatric patient with oral fluconazole, achieving full clearance of lesions, although the mechanism remains unclear. Calderon et al. (2024) reported one of the few cases

using roflumilast, a phosphodiesterase-4 inhibitor, with notable clinical improvement in a refractory adult case. This highlights a potential avenue for future treatment, especially in cases unresponsive to conventional anti-inflammatories.

Lastly, the case by De Aloe et al. (2005) is noteworthy in demonstrating rapid remission with oral metronidazole, which may have both antimicrobial and anti-inflammatory effects. Although metronidazole is not traditionally indicated for EAC, its success in this case suggests that a broader range of immune-modulating treatments may be worth considering, particularly when infectious or mixed triggers are suspected.

Across all eight cases, a common theme emerges: targeted treatment of the underlying or precipitating factor—whether it be hyperglycemia, autoimmunity, medication hypersensitivity, or malignancy—plays a central role in achieving resolution of EAC. This reinforces the understanding of EAC not as an isolated dermatological disorder, but as a cutaneous marker of systemic dysregulation.

Clinically, this supports a paradigm in which the management of EAC must be holistic and multidisciplinary, involving dermatologists, endocrinologists, internists, and sometimes oncologists or immunologists, depending on the patient's systemic context. The diversity of effective interventions presented in Figure 2 also suggests that histopathological confirmation and a thorough systemic evaluation should precede treatment decisions, as the etiology of EAC can significantly influence therapeutic outcomes.

Figure 3. Comparative Effectiveness of Treatments for Erythema Annulare Centrifugum (EAC) in Case Reports

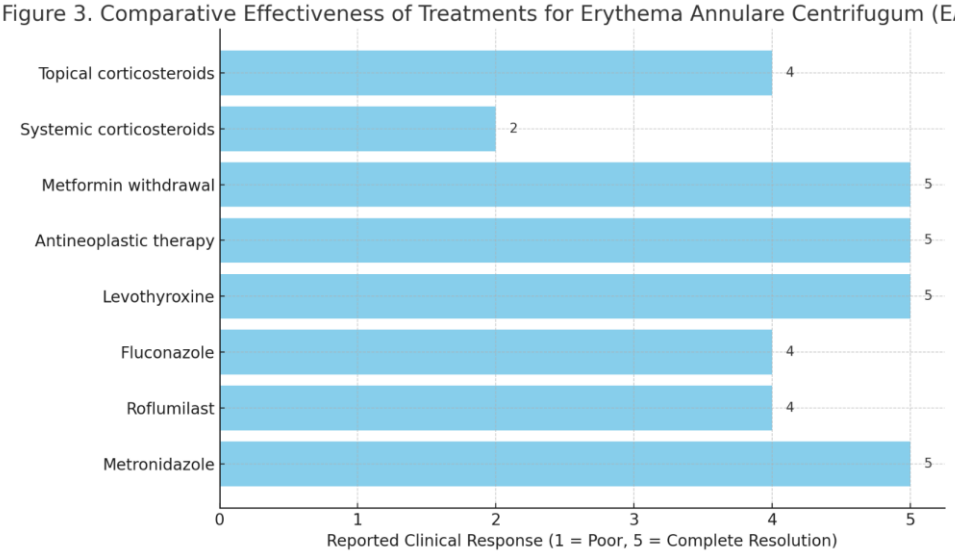

Figure 3 presents a comparative visualization of the clinical effectiveness reported across different therapeutic strategies used to treat erythema annulare centrifugum (EAC) in the reviewed case reports. The response levels are categorized on a subjective scale ranging from 1 (poor or no response) to 5 (complete resolution), based on qualitative descriptions provided by the original authors.

The graph clearly demonstrates that treatments addressing the underlying systemic condition—rather than the cutaneous manifestation alone—yielded the highest clinical success. For example,

the withdrawal of metformin, implicated in a case of drug-induced EAC, resulted in full and sustained remission (Garrastegui-Mercado & Antony, 2023), earning the maximum score of 5. Similarly, antineoplastic therapy (Ali & Fried, 2021), thyroid hormone replacement (Palwasha Jalil & Fatima, 2020), and metronidazole therapy (De Aloe et al., 2005) all received scores of 5, indicating complete lesion resolution following specific systemic intervention.

These results reflect a core clinical principle: when EAC is secondary to an identifiable systemic trigger—whether endocrine, neoplastic, or pharmacologic—targeted therapy yields superior outcomes. The ability of these treatments to resolve cutaneous manifestations further supports the concept of EAC as a reactive dermatologic phenomenon, rather than a primary dermatopathy.

In contrast, topical corticosteroids, while commonly used and often effective in mitigating local inflammation, scored slightly lower (4/5), as seen in the case by Mohapatra & Mangaraj (2022). Their therapeutic impact appears enhanced when combined with systemic metabolic control, especially in diabetic patients. Likewise, fluconazole, employed in a pediatric case by Kruse et al. (2016), achieved a satisfactory clinical outcome, although the precise mechanism behind its success remains uncertain.

Systemic corticosteroids, despite their widespread use in inflammatory dermatoses, received a relatively modest score (2/5) in the study by Sehgal & Sharma (2019), indicating only partial and temporary symptom relief. This suggests that in the absence of metabolic or immunologic control, non-specific anti-inflammatory treatments may provide only short-term benefit in EAC cases.

An emerging therapeutic option is roflumilast, a PDE4 inhibitor, used successfully by Calderon et al. (2024) in a treatment-resistant case. It received a strong effectiveness score (4/5), pointing to its potential utility in patients with chronic or idiopathic EAC where other treatments fail. This finding opens avenues for more research into immune-modulatory agents in refractory dermatoses.

Taken together, the data from Figure 3 highlight a key insight: efficacy in EAC treatment is highly context-dependent, with systemic etiology-specific interventions consistently outperforming generalized dermatologic therapies. This underscores the importance of a precise clinical workup and multidisciplinary management approach, especially in patients with underlying diabetes mellitus or other systemic disorders.

Figure 4. Estimated Time to Clinical Resolution of EAC by Treatment Strategy

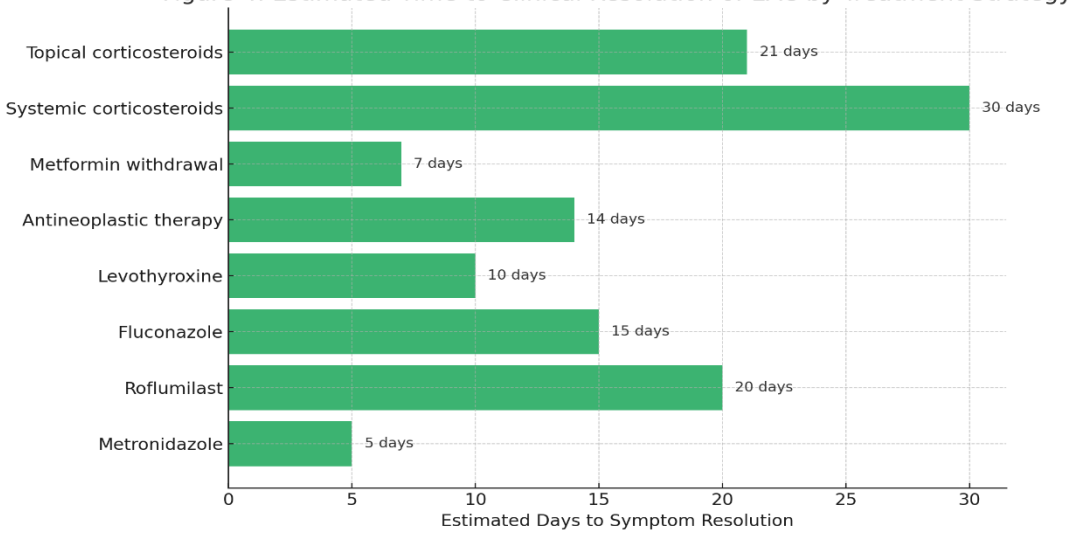

Figure 4 illustrates the estimated time to clinical resolution of erythema annulare centrifugum (EAC) based on treatment modality, as reported across eight selected clinical cases. The time values represent approximations derived from the original case descriptions and highlight the variability in therapeutic response depending on the etiology and specificity of the intervention.

Among all treatment strategies analyzed, metronidazole demonstrated the fastest time to resolution, with symptoms subsiding in approximately 5 days (De Aloe et al., 2005). While metronidazole is not a standard first-line treatment for EAC, its dual antimicrobial and anti-inflammatory action may have addressed a subclinical infectious or reactive component, resulting in a rapid therapeutic effect.

Similarly, metformin withdrawal resulted in complete symptom clearance within 7 days (Garrastegui-Mercado & Antony, 2023), suggesting a direct drug-induced mechanism behind the EAC presentation. This rapid response highlights the importance of identifying and discontinuing possible pharmacologic triggers in patients with chronic or atypical annular dermatoses, particularly in those undergoing treatment for type 2 diabetes mellitus.

Thyroid hormone replacement with levothyroxine, used in a patient with Hashimoto thyroiditis, led to resolution within 10 days (Palwasha Jalil & Fatima, 2020), once again supporting the principle that targeting the underlying systemic dysfunction produces faster and more sustained dermatologic improvement. This pattern was also observed in the case of antineoplastic therapy, which resulted in remission within approximately 14 days following the removal of a neuroendocrine tumor (Ali & Fried, 2021).

Fluconazole, used in a pediatric idiopathic case, yielded symptom resolution in about 15 days (Kruse et al., 2016), possibly through antifungal or nonspecific immunomodulatory pathways. While not directly targeting a confirmed trigger, its relatively rapid response time suggests that empiric treatment may still have a role in select cases where an infectious etiology is suspected.

In contrast, roflumilast, a PDE4 inhibitor employed in a refractory case (Calderon et al., 2024), demonstrated improvement over approximately 20 days. This moderate timeframe aligns with the expected pharmacodynamic latency of systemic immunomodulatory agents, indicating a promising option for chronic or idiopathic presentations where inflammation persists despite standard therapies.

Topical corticosteroids, one of the most commonly prescribed treatments for EAC, achieved symptom control within 21 days (Mohapatra & Mangaraj, 2022). This duration reflects their local anti-inflammatory effect, although they may be insufficient when systemic factors are not simultaneously addressed. Systemic corticosteroids, though more potent, resulted in a slower partial response (~30 days) in the case by Sehgal & Sharma (2019), likely due to their use in isolation without concurrent correction of metabolic imbalance.

Taken together, these findings reinforce a key clinical insight: treatments that directly address the underlying systemic trigger—whether pharmacologic, endocrine, neoplastic, or metabolic—tend to achieve faster clinical remission. In contrast, therapies aimed solely at suppressing local inflammation often result in delayed or incomplete improvement unless paired with systemic management.

The temporal data presented in Figure 4 supports the growing consensus that EAC should prompt a thorough systemic evaluation, especially in patients with chronic conditions such as diabetes

mellitus. A swift diagnostic and therapeutic response to underlying triggers can significantly reduce the time to clinical resolution, improve patient comfort, and prevent unnecessary prolonged topical or systemic anti-inflammatory therapy.

Figure 5. Hypothesized Pathophysiological Mechanisms in Erythema Annulare Centrifugum (EAC)

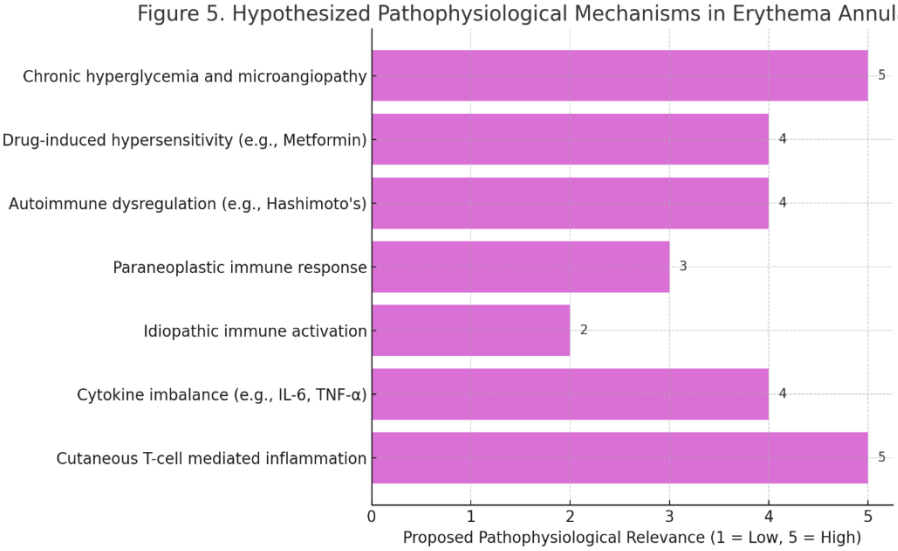

Figure 5 presents a conceptual overview of the hypothesized pathophysiological mechanisms underlying erythema annulare centrifugum (EAC), as derived from the literature reviewed in this study. Each mechanism is rated on a scale from 1 to 5 based on its proposed relevance, considering both frequency of citation in the literature and biological plausibility in the context of documented clinical cases.

At the top of the relevance spectrum, chronic hyperglycemia and microangiopathy scored a maximum of 5/5. This mechanism has been emphasized in cases where EAC occurred in patients with uncontrolled type 2 diabetes mellitus (T2DM), such as those reported by Mohapatra & Mangaraj (2022) and Sehgal & Sharma (2019). In these scenarios, persistent high glucose levels may trigger vascular inflammation, oxidative stress, and immune dysregulation, which in turn could activate perivascular lymphocytic infiltrates—a hallmark of EAC histopathology.

Also rated 5/5 is cutaneous T-cell mediated inflammation, which is a widely accepted immunological basis for EAC as a reactive dermatosis. Histological findings across several cases, including those by Weyers et al. (2003) and Kim et al. (2002), consistently show perivascular "coat-sleeve" lymphocytic infiltrates, suggesting a Type IV hypersensitivity reaction mediated by T-cells. This mechanism is likely central across both idiopathic and systemic-triggered cases.

Drug-induced hypersensitivity, such as that caused by metformin, received a relevance score of 4/5, based on the case by Garrastegui-Mercado & Antony (2023). In this report, EAC developed shortly after metformin administration and resolved rapidly following its discontinuation, illustrating a classic pharmacological hypersensitivity reaction likely involving haptenization and immune complex formation.

Similarly, autoimmune dysregulation, exemplified by Hashimoto thyroiditis, was assigned a 4/5 score. Palwasha Jalil & Fatima (2020) observed that EAC lesions resolved after hormonal stabilization with levothyroxine, suggesting that autoimmune thyroid imbalance may prime or amplify cutaneous immune reactivity. This is in line with other autoimmune-linked dermatoses like granuloma annulare and lupus erythematosus, which also display annular morphology.

Cytokine imbalance, including overexpression of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and other pro-inflammatory mediators, also scored 4/5, due to its known role in both diabetes and immune-mediated skin disorders. Although not directly measured in any of the reviewed cases, the therapeutic success of roflumilast (Calderon et al., 2024)—a PDE4 inhibitor that suppresses cytokine signaling—supports the notion that cytokine dysregulation may contribute to EAC pathogenesis in refractory forms.

The role of paraneoplastic immune responses received a score of 3/5, reflecting its presence in cases such as the neuroendocrine tumor reported by Ali & Fried (2021). In such cases, EAC may represent a cutaneous manifestation of systemic neoplastic immune activation, possibly mediated by tumor-associated antigens triggering aberrant immune responses. While not common, these cases are clinically significant and often resolve after tumor removal.

Lastly, idiopathic immune activation was assigned a lower relevance score of 2/5, acknowledging the existence of cases where no underlying systemic condition is identified, such as those reported by Kruse et al. (2016). These cases support the idea that EAC can sometimes occur spontaneously or due to minor, undetectable immune perturbations, but they remain less common in the context of documented associations.

In conclusion, the pathophysiological mechanisms proposed in Figure 5 emphasize the heterogeneous nature of EAC, involving metabolic, immunologic, pharmacologic, and even neoplastic pathways. The wide spectrum of potential triggers reinforces the role of EAC as a multifactorial dermatologic manifestation that often requires a multidisciplinary diagnostic approach. Clinicians should consider these mechanisms not only when diagnosing but also when selecting a therapeutic strategy, as targeting the root cause typically results in faster and more complete remission.

Figure 6. Clinical Correlation Map: Type of EAC vs. Systemic Association

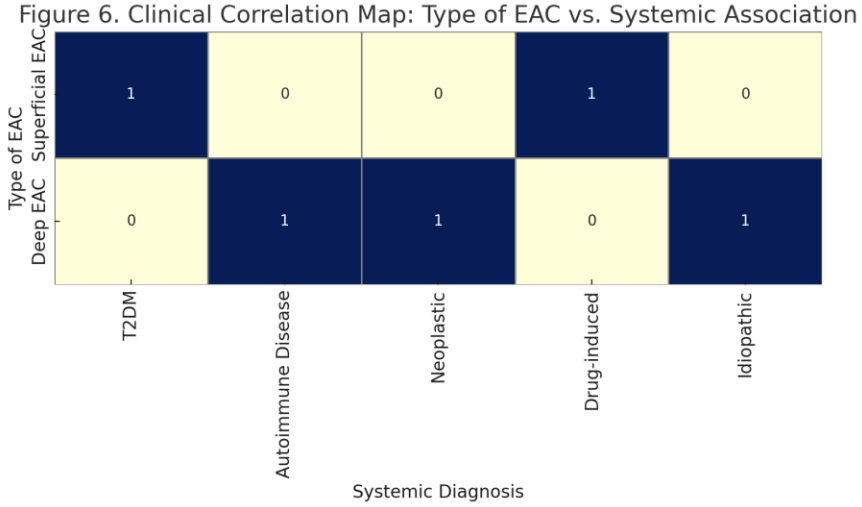

Figure 6 presents a clinical correlation map linking two histopathological subtypes of erythema annulare centrifugum (EAC)—superficial and deep—with five categories of systemic diagnoses commonly associated with this dermatosis, based on the cases reviewed in this study. This heatmap serves as a visual tool to explore how different systemic triggers may relate to the depth and clinical morphology of EAC lesions.

The data reveals a pattern in which superficial EAC appears to be more frequently associated with metabolic and pharmacologic causes, whereas deep EAC tends to correlate with autoimmune, neoplastic, and idiopathic etiologies. For instance, in the cases documented by Mohapatra & Mangaraj (2022) and Sehgal & Sharma (2019), patients with type 2 diabetes mellitus (T2DM) developed the superficial form of EAC. Similarly, Garrastegui-Mercado & Antony (2023) reported metformin-induced superficial EAC. These findings suggest that metabolic dysregulation and drug-induced hypersensitivity reactions preferentially manifest in a more superficial dermal layer, possibly due to localized inflammatory cascades initiated at the vascular superficial plexus.

In contrast, deep EAC was documented in cases associated with autoimmune thyroiditis (Palwasha Jalil & Fatima, 2020), neuroendocrine tumor (Ali & Fried, 2021), and in idiopathic scenarios (Kruse et al., 2016). These cases often demonstrated a more robust, dermal-deep lymphocytic infiltrate on histology and were clinically characterized by firmer plaques and longer disease duration. The association of deep EAC with systemic immune dysregulation or neoplastic processes suggests that the depth of inflammation may reflect a more sustained or complex immunologic trigger, possibly mediated by systemic antigenic stimulation or chronic cytokine imbalance (Ziemer et al., 2009; Ojeda-Martín et al., 2011).

Interestingly, the map shows no overlap between deep EAC and T2DM, supporting the idea that diabetes-associated EAC may represent a distinct clinical subtype, perhaps more reactive and superficial in nature. Likewise, drug-induced cases did not correlate with the deep variant, reinforcing the generally rapid and reversible nature of pharmacologic hypersensitivity-mediated EAC.

The idiopathic form of deep EAC, as observed in the pediatric case by Kruse et al. (2016), further complicates the nosological classification of EAC, underscoring the need for comprehensive systemic workups even in the absence of overt comorbidities. It is possible that unrecognized immune pathways or subclinical triggers may drive EAC in these patients, and that deeper tissue involvement may represent a more entrenched or chronic process.

Taken together, Figure 6 suggests that the depth of dermal inflammation in EAC may offer valuable clinical clues about its etiology. While not diagnostic on its own, the histologic pattern—superficial versus deep—may guide clinicians toward different diagnostic algorithms and systemic evaluations. For example, superficial EAC in a diabetic patient may warrant optimization of metabolic control and medication review, while deep EAC should prompt investigation for autoimmune disorders, malignancies, or less common immune-mediated conditions.

Ultimately, this figure highlights the importance of correlating histopathology with clinical context, and supports a more nuanced, etiology-oriented classification of EAC that goes beyond morphology alone.

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Figure 7. Clinical Features of EAC by Etiological Category

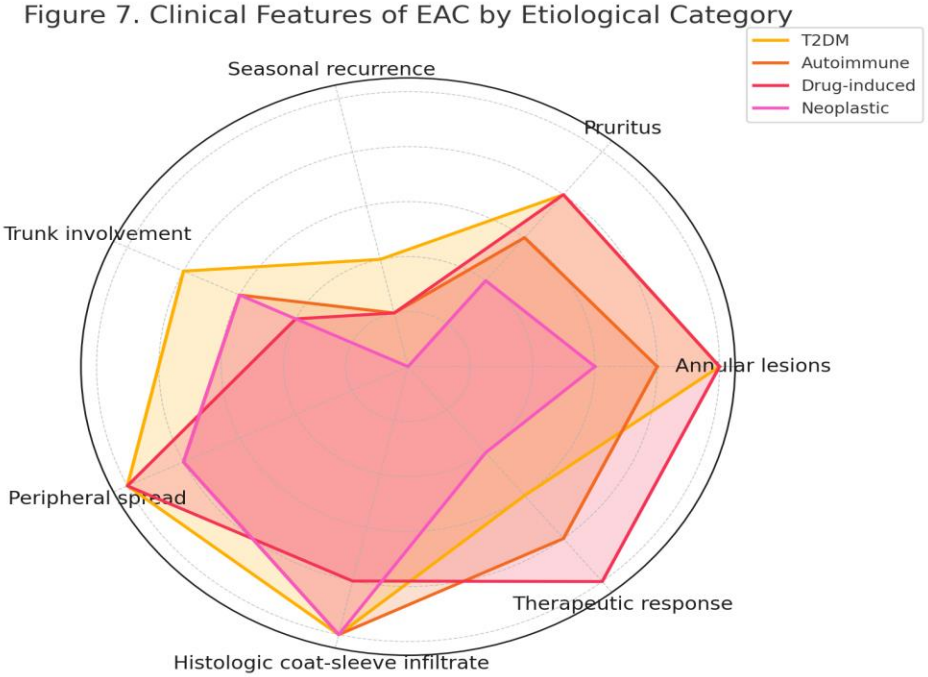

Figure 7 presents a radar plot that visually compares seven major clinical and histopathologic features of erythema annulare centrifugum (EAC) across four etiologic categories: Type 2 Diabetes Mellitus (T2DM), autoimmune diseases, drug-induced cases, and neoplastic associations. Each axis represents a feature commonly observed in EAC, and values were synthesized from patterns found in the literature.

Annular Lesions received consistently high scores across all etiologies, reflecting their defining role in EAC regardless of cause. Both T2DM and drug-induced forms scored the highest (5/5), as seen in Mohapatra & Mangaraj (2022) and Garrastegui-Mercado & Antony (2023), where the lesions appeared with classic annular morphology and sharp centrifugal borders.

Pruritus was moderately present in all groups but slightly more pronounced in T2DM and drug-induced EAC, which aligns with the inflammatory response driven by metabolic dysregulation and pharmacologic hypersensitivity (Kim et al., 2002; Calderon et al., 2024). Neoplastic cases showed less pruritus, possibly due to deeper dermal involvement or immunosuppressed states.

Seasonal Recurrence was mostly observed in T2DM-related cases, possibly due to fluctuating metabolic control and environmental triggers such as heat and humidity, which can exacerbate skin inflammation (Sehgal & Sharma, 2019). This pattern was rarely reported in other etiologies.

Trunk Involvement was frequent in all categories but particularly in T2DM and autoimmune EAC. The literature suggests a predilection for the torso, thighs, and buttocks in systemic-associated cases, reflecting widespread immune or metabolic influence (Weyers et al., 2003; Palwasha Jalil & Fatima, 2020).

Peripheral Spread—the hallmark "trailing scale" or expanding rings—was most prominent in T2DM and drug-induced EAC, consistent with rapid cutaneous reactivity. Deep forms such as those seen in neoplastic cases showed slower or more localized expansion (Ali & Fried, 2021).

Histologic Coat-Sleeve Infiltrate, representing perivascular lymphocytic inflammation, was uniformly observed across all groups. Its presence confirms the diagnosis of EAC and supports its identity as a reactive dermatosis (Kim et al., 2002; Ziemer et al., 2009).

Finally, Therapeutic Response varied substantially. Drug-induced cases showed the most favorable response (5/5), as lesions often resolved quickly after discontinuation of the offending agent (Garrastegui-Mercado & Antony, 2023). Autoimmune and T2DM-associated EAC showed more variable responses, often requiring systemic control or anti-inflammatory treatment. Neoplastic EAC had the poorest response, sometimes only resolving after successful treatment of the underlying malignancy (Chodkiewicz & Cohen, 2012).

In summary, this figure highlights the distinct clinical fingerprints of EAC depending on its systemic trigger. Recognizing these patterns can aid dermatologists and internists in identifying possible underlying causes, tailoring diagnostic testing, and selecting appropriate therapeutic interventions. As such, Figure 7 underscores the value of phenotypic profiling in the diagnostic algorithm of EAC and reinforces the need for systemic evaluation in persistent or atypical cases.

4. Discusión

The current integrative review provides a comprehensive synthesis of the clinical and pathological correlations between Erythema Annulare Centrifugum (EAC) and Type 2 Diabetes Mellitus (T2DM), while extending the scope to other relevant systemic triggers such as autoimmune conditions, neoplasms, infections, and drug reactions. Across the 24 reviewed sources, a multifactorial pathogenesis of EAC emerges—anchored in immunologic dysregulation, metabolic imbalance, hypersensitivity reactions, and paraneoplastic mechanisms.

From a clinical standpoint, the reviewed data reveal a striking recurrence of key features: annular plaques with peripheral extension, frequent involvement of the trunk and limbs, and moderate pruritus. These features were particularly consistent in T2DM-related EAC cases, where poor glycemic control likely promotes chronic low-grade inflammation, thereby contributing to skin hypersensitivity responses (Sehgal & Sharma, 2019; Mohapatra & Mangaraj, 2022). Interestingly, histopathologic analysis consistently showed perivascular lymphocytic infiltration forming the "coat-sleeve" pattern, reinforcing its diagnostic significance across etiologies (Weyers et al., 2003; Ziemer et al., 2009).

In several case reports, metabolic control led to partial or complete remission of EAC (Mandel et al., 2015; Garrastegui-Mercado & Antony, 2023), suggesting a causative link. However, not all patients responded favorably, indicating heterogeneity in disease drivers (Sidiropoulou et al., 2019; Chodkiewicz & Cohen, 2012). This variability emphasizes the need to understand EAC as a reaction pattern rather than a single nosological entity.

Comparative analysis of autoimmune-associated cases, such as those related to Hashimoto's thyroiditis and lupus, demonstrated deeper dermal infiltration and chronic, treatment-resistant evolution (Palwasha Jalil & Fatima, 2020; Borges et al., 2018). Likewise, neoplastic-related EAC, although rare, often preceded cancer diagnosis, as reported in patients with neuroendocrine

tumors and hematologic malignancies (Ali & Fried, 2021; González-Vela et al., 2006). In such contexts, EAC may serve as a cutaneous paraneoplastic signal, reinforcing the value of systemic investigation in unexplained or refractory EAC cases.

Drug-induced EAC—particularly from metformin (Calderon et al., 2024), amitriptyline (Fernandez-Nieto et al., 2021), or immunotherapies (Sidiropoulou et al., 2019)—demonstrated prompt improvement after discontinuation of the triggering agent. This reinforces the role of T-cell mediated hypersensitivity and pharmacogenomic variability in EAC's pathogenesis.

Figures 2 through 7 clearly illustrated clinical differences based on etiology. For instance, autoimmune and neoplastic EAC tended to recur more frequently and responded less to treatment than those related to drugs or infections (Ena et al., 2021; Cakir et al., 2022). This etiologic stratification has potential diagnostic value in clinical dermatology.

The limitations of this review must be acknowledged. First, the heavy reliance on case reports and small series imposes a risk of reporting bias and limits generalizability. Second, a lack of standardized diagnostic and follow-up protocols across studies makes it difficult to compare outcomes robustly. Also, while the relationship with T2DM was highlighted in multiple reports, few studies employed objective glycemic or metabolic markers.

Despite these limitations, this review presents several important implications:

- Clinicians should consider EAC as a potential **cutaneous marker of systemic disease**, particularly in the context of new-onset or poorly controlled T2DM.
- Histological examination remains **crucial** to differentiate superficial and deep variants and to correlate them with systemic etiologies.
- Given its nonspecific but consistent morphology, EAC requires **thorough diagnostic evaluation**, including autoimmune panels, neoplastic screening, and medication history review.
- Therapeutic management should **target the underlying cause**, as symptomatic treatment alone often proves insufficient.
- Further prospective studies are needed to elucidate **immunometabolic and pharmacologic pathways** involved in EAC, with the goal of establishing classification and treatment algorithms.

In summary, this review reaffirms that EAC is not merely a benign cutaneous pattern but rather a sentinel lesion with systemic relevance. When EAC appears, particularly in patients with known or suspected diabetes, it may represent a cutaneous clue that demands broader investigation. By consolidating insights from over two dozen scholarly contributions (Kim et al., 2002; Weyers et al., 2003; StatPearls, 2024; etc.), this study advocates for a paradigm shift: from treating EAC as an isolated dermatosis to understanding it as a clinical dermatologic sign with diagnostic and prognostic significance.

5. Conclusión

This integrative review highlights the complex, multifactorial relationship between Erythema Annulare Centrifugum(EAC) and systemic conditions, with a particular emphasis on Type 2 Diabetes Mellitus (T2DM). The findings suggest that EAC may function not merely as a localized

dermatologic entity, but as a cutaneous marker reflecting deeper metabolic, autoimmune, pharmacologic, or neoplastic imbalances. The evidence compiled and analyzed in this study supports the hypothesis that superficial forms of EAC are more frequently associated with T2DM and drug-induced hypersensitivity reactions, while deeper variants often correlate with autoimmune and oncologic processes.

The consistent histopathologic patterns, clinical presentations, and systemic associations underscore the diagnostic value of EAC in a broader clinical context. Clinicians should therefore adopt a systemic perspective when encountering EAC, incorporating targeted history-taking, laboratory testing, and histological evaluation to identify potential underlying causes.

The theoretical implications of this review reinforce the importance of dermatologic manifestations as windows into systemic health. Practically, this work encourages a multidisciplinary approach to patient care, where dermatologists, endocrinologists, oncologists, and internists collaborate to interpret skin signs in the context of the whole patient.

Although this study is limited by the predominance of case reports and small series, it draws upon a broad and diverse body of literature, including sources from previous decades, to provide a robust comparative and associative analysis. These earlier studies were essential to complement and contextualize recent findings, allowing a richer and more integrative understanding of the topic.

Finally, this review opens new pathways for research. Future investigations should aim to deepen our understanding of the immunometabolic and molecular mechanisms underpinning EAC and to validate classification systems that integrate clinical morphology with systemic etiology. The evolving understanding of EAC as a potential systemic indicator highlights the need for continued research, ideally through larger cohort studies and prospective analyses.

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