

NEWS, VIEWS, AND REVIEWS

On the Nod: A Scoping Review on Proposed Management Strategies for Erythema Nodosum

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INTRODUCTION

Erythema nodosum (EN) is the most common form of panniculitis, classically presenting as tender, erythematous subcutaneous nodules on the extensor surfaces of the lower extremities. Systemic symptoms, including fevers, chills, and arthralgias, may also accompany the cutaneous manifestations.[1] EN typically occurs between the second and fourth decades of life, and is up to six times more common in females.[2] EN is thought to be a delayed hypersensitivity reaction, and there is an extensive list of triggers, including infectious agents, medications, underlying inflammatory diseases, malignancy, and hormonal states. Nevertheless, the trigger remains unidentified in up to 50% of cases.[1] EN is often self-limited, with symptoms typically peaking in 1-2 weeks and resolving over 1-12 weeks. However, there is also a subset of patients who experience chronic, recurrent EN, which can last for several years.[3] While treatment should be directed toward the trigger in cases with a known etiology, in all cases, additional treatments are often warranted, given the exquisitely tender nature of EN lesions. Herein, we will discuss the current landscape of therapeutic interventions for EN.

MANAGEMENT STRATEGIES

Non-pharmacological interventions

Bed rest, leg elevation, and leg compression are commonly recommended adjuvant therapies for EN.[1,3] The pain in EN is thought to be in part caused by edema-induced pressure on surrounding tissues, and bed rest with elevation of the legs reduces this pressure by increasing venous return.[1] While there are no guidelines regarding duration and frequency, some authors have recommended elevating the legs for at least 30 minutes twice daily.[1] For the same reason, patients should also wear support stockings or pressure bandages during periods of activity.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a first-line therapy for EN, relieving pain and inflammation by inhibiting cyclooxygenase production. Specifically, naproxen 1000 mg daily for 2-3 weeks, oxyphenbutazone 400 mg daily, and indomethacin 100-150 mg daily, the latter two for unspecified durations, have all demonstrated efficacy in alleviating discomfort.[3] Comparative studies are lacking, though the authors of one article recommended starting with indomethacin and using ibuprofen or naproxen secondarily.[1] NSAIDs are cost-effective and accessible, though they should be avoided in those with renal disease and used cautiously in patients with gastritis and esophagitis.

Potassium Iodide (KI)

KI has been used to successfully treat many dermatologic conditions, although its mechanism of action remains poorly understood. Studies demonstrate that it inhibits neutrophil chemotaxis and interferes with neutrophil oxidative burst.[1] Additionally, KI causes mast cells to release heparin, which may play a role in EN management by suppressing delayed hypersensitivity reactions.[2] In a study of 15 EN patients treated with KI, 300 mg three times daily, 11 experienced an 'excellent' response, with subjective symptom improvement within 24 hours and complete lesion resolution after 10-14 days.[4] Patients who were administered KI closest to EN onset had the best responses. While effective in managing EN, KI can be accompanied by rare but serious side effects, thus, it must be avoided or used with extreme caution in certain patient populations. Patients with a history of thyroid disease or taking medications such as lithium and amiodarone can be at risk of hypothyroidism and goiter. Additionally, prolonged use of KI may result in potassium toxicity, especially in patients on potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, or those with chronic renal disease.[1]

Colchicine

Colchicine is an anti-inflammatory agent that functions by arresting microtubule polymerization, interfering with neutrophil chemotaxis. In a retrospective case series of 12 patients with long-standing EN treated with colchicine 0.6 mg twice daily for a mean duration of 8 months, 8 patients experienced improvement, 6 of whom completely cleared.[5] Colchicine has also been found to be particularly effective in managing EN in patients with Behcet's syndrome, particularly females. In a double-blind trial of colchicine vs. placebo in 116 patients with Behcet's syndrome, 79% of female patients taking colchicine 1-2 mg daily versus 39% of females taking placebo were clear of EN lesions after 24 months (P=0.004).[6] These data suggest that colchicine may be useful in patients with chronic, recalcitrant EN or co-existing Behcet's syndrome.

Hydroxychloroquine

Compared to other treatments, evidence supporting hydroxychloroquine for EN management is limited, with only two case reports demonstrating its efficacy. Although the exact anti-inflammatory mechanism of hydroxychloroquine is unclear, interference with antigen presentation to macrophages has been proposed.[7] The first report described a 52-year-old female with a 7-year history of EN that was unresponsive to NSAIDs and partially responsive to oral prednisolone. After flaring with cessation of prednisolone, she was started on hydroxychloroquine 200 mg twice daily with prednisolone 15 mg once daily. After 8 weeks, improvement was noted, and the steroid was discontinued.[8] She sustained improvement on hydroxychloroquine monotherapy, which was tapered to 200 mg daily and discontinued after 7 months. In the year following discontinuation, occasional flares occurred, but were controlled with 7-day courses of hydroxychloroquine 200 mg daily. The second report described a 38-year-old female with a greater than 20-year history of recurrent EN that was similarly responsive to oral prednisone but flared upon discontinuation. After initiation of hydroxychloroquine 200 mg daily, she experienced a significant reduction in lesion count and pain, which was sustained at 6-month follow-up.[7] In both cases, hydroxychloroquine was very well tolerated. These cases support hydroxychloroquine's utility in chronic, recurrent EN, though larger studies are needed to verify its efficacy.

Tumor necrosis factor-α inhibitors (TNFis)

TNFis are well-regarded for their ability to treat several inflammatory dermatoses and are also effective in reducing mucosal inflammation in patients with inflammatory bowel disease (IBD).[9] Studies have started to investigate whether TNFis may also improve extraintestinal manifestations of IBD, such as EN, one of the most common cutaneous sequelae of IBD. Both infliximab and adalimumab have demonstrated efficacy in treating cases of EN associated with IBD in young females.[9,10] Notably, etanercept and adalimumab have also shown benefit in treating EN that was not associated with IBD. Etanercept, dosed at 25 mg twice weekly, cleared lesions within 4 months in a 22-year-old patient with a 5-year history of idiopathic EN, who was previously unresponsive to KI, NSAIDs, methotrexate, dapsone, and prednisone.[11] Etanercept was also effective, when dosed at 50 mg biweekly, in a patient with *BCR-ABL*-positive chronic myeloid leukemia with extremely painful tyrosine kinase inhibitor-induced EN.[12] Adalimumab successfully treated a 79-year-old patient with chronic EN unresponsive to NSAIDs, antimalarials, and colchicine. This patient was initially responsive to corticosteroids but relapsed with tapering and over time, developed vertebral crushing due to prolonged steroid use. Adalimumab 40 mg biweekly was started, and at 7-month follow-up, the patient reported no flares.[13] While the current data is limited to case reports, TNFis hold promise as a safe and effective therapy in refractory cases of EN regardless of association with IBD.

Other treatments

As mentioned above, systemic corticosteroids such as prednisone and prednisolone have been used with success in patients with EN; however, in the vast majority of cases, disease relapses after treatment cessation, and repeated, prolonged steroid use is associated with multiple adverse effects.[7,8] For this reason, corticosteroids are rarely indicated in the management of EN. Dapsone has also been employed to treat EN. One retrospective case series described three patients with recurrent, recalcitrant EN who responded to dapsone 50-75 mg daily, but all three patients were on concurrent therapies – prednisone, hydroxychloroquine, and infliximab, respectively – making it difficult to determine the individual efficacy of dapsone.[14]

CONCLUSION

There are many therapeutic options for EN; however, the body of supporting evidence remains extremely limited, making it challenging to determine which management strategies are superior. Apart from NSAIDs, which are a mainstay of symptomatic EN treatment, potassium iodide, colchicine, and TNFis are the treatments associated with the highest number of successful cases. While there are fewer reports on the efficacy of hydroxychloroquine, its success in chronic, treatment-refractory cases makes it a promising last resort. Ultimately, further research is needed to understand which therapies are most effective and suitable for specific patient profiles.

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