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Treatment of foreign body granulomas with combined enzyme therapy

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Abstract

Introduction: Granulomas are focal aggregates of inflammatory cells that form in response to a persistent inflammatory stimulus. Available therapies include surgical and nonsurgical management, and current evidence is based on case series or case reports.
Methods: Two case reports of foreign body granulomas treated with a combination of recombinant enzymes (hyaluronidase, collagenase, and lipase of bacterial origin) are presented.
Results: Following three sessions of combined enzyme treatment with a scheduled protocol, both patients showed clinical improvement without any reported adverse events.
Conclusions: Combined enzyme therapy is an effective, safe, minimally invasive, innovative approach for the treatment of foreign body granulomas.

Keywords: granuloma, combined enzyme treatment, collagenase, hyaluronidase, lipase

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Introduction

Granulomas are localized clusters of macrophages that may or may not include other inflammatory cell types, typically forming in response to a persistent inflammatory stimulus (1). When the stimulus is particulate—whether living or nonliving—granuloma formation generally indicates that initial phagocytic cells were unable to eliminate it, representing a failure in the initial immune response (2). Virtually any foreign material has the potential to trigger a granulomatous reaction. As granulomas evolve, they may develop fibrosis, necrosis, or both. Fibrotic processes are mediated by cytokines such as transforming growth factor beta 1 (TGF-β1), interleukin 13, and vascular endothelial growth factor (VEGF) (2). Clinically, foreign body granulomas often appear as erythematous, brownish, or purpuric papules, nodules, or plaques. Certain foreign materials, such as tattoo metals, can also lead to pigmentary changes (3). Current therapeutic approaches include Q-switched lasers, picosecond laser technologies, and topical agents such as tacrolimus and imiquimod (4). Notably, the use of recombinant enzyme combinations—specifically collagenases, hyaluronidases, and lipases—is gaining traction as a minimally invasive treatment for various conditions, including scars, cellulite, and submental fullness (5). Given that fibrosis is a common feature across these conditions, including granulomas (2, 5), we report the successful treatment of foreign body granulomas using a combined enzyme approach involving collagenase G/H PB220, hyaluronidase PB300, and lipase PB500 (Proteos Biotech®, Madrid, Spain).

Methods

We reviewed data from medical records of patients diagnosed with granulomas that were treated with combined enzyme therapy—collagenase G/H PB220, hyaluronidase PB300, and lipase PB500—in a private clinical setting. Information was collected on treatment regimens, clinical outcomes, and self-reported safety observations.

Results

Case 1: A 35-year-old female patient, with an otherwise unremarkable medical history aside from two recent tattoos, presented with raised, irregular, erythematous lesions on both forearms. Histological examination following a skin biopsy confirmed the presence of a foreign body granuloma (Fig. 1). After obtaining informed consent, treatment with a combination of collagenase G/H PB220, hyaluronidase PB300, and lipase PB500 was initiated. The lyophilized formulations were reconstituted and administered intralesionally—1.5 ml of each enzyme—combined with 2% lidocaine, using a 30° blanching technique. Three treatment sessions were scheduled at 20-day intervals. A marked clinical improvement was observed following the treatment course (Fig. 2). A repeat biopsy performed 30 days after the final session showed no residual granuloma, along with reduced interpapillary ridges and ascending dermal blood vessels.

Case 2: A 75-year-old female patient presented with an elevated lesion in the glabellar region, clinically consistent with a granuloma. Ultrasound revealed three focal echogenic areas with characteristic "snowstorm" artifacts located in the dermis and hypodermis. The largest lesion, measuring 14 mm × 11 mm, was at the left ciliary margin (Fig. 3). No changes in vascularization were noted on color Doppler imaging. Although the etiology could not be determined from the patient's history and clinical findings, ultrasound features were suggestive of a siliconoma. Following informed consent, the patient underwent three sessions of combined enzyme therapy—collagenase G/H PB220, hyaluronidase PB300, and lipase PB500—administered at 20-day intervals. One month after the final session, follow-up ultrasound showed a reduction in the size of all lesions. Clinically, the patient showed complete resolution (Fig. 4), with no recurrences observed during 1 year of follow-up. A repeat ultrasound was not deemed necessary at 12 months due to the favorable clinical outcome. No adverse events were reported by either patient.

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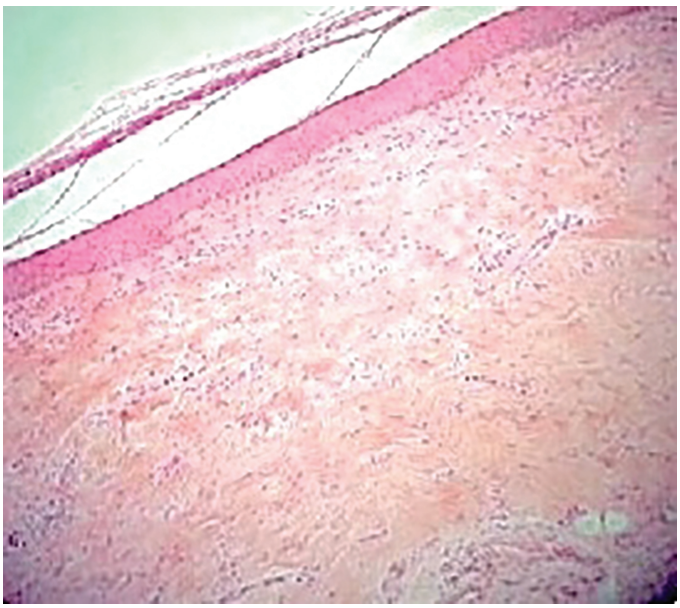

Figure 1 | Lesion microscopy: an infiltrate composed of lymphocytes, histiocytes, and multinucleated giant cells suggestive of foreign body granuloma is observed throughout the dermis (hematoxylin and eosin 10×, conventional light microscope).

Discussion

In our patients, the use of combined enzyme therapy—including a collagenase, a hyaluronidase, and a lipase—was associated with clinical improvement of foreign body granulomas and demonstrated a favorable tolerability profile. Even though accurate diagnosis of granulomatous reactions typically relies on histopathological examination, imaging techniques such as ultrasound may also be helpful in certain cases (4). Although several treatment strategies have been described, most are supported only by case reports or small case series (4). Surgical excision is rarely considered a first-line option because complete removal of a granuloma is often unfeasible due to its invasive nature and the lack of clear demarcation from surrounding tissue (6). This underscores the need for innovative nonsurgical therapeutic approaches.

Combined enzyme therapy has been proposed for a variety of conditions based on shared pathogenic mechanisms, including epidermoid cysts, facial rejuvenation, submental fullness, and edematous fibrosclerotic panniculopathy (7, 8). In fibrotic tissue, recombinant collagenases enzymatically degrade collagen into simple peptides without requiring additional enzymes such as gelatinases. These collagen breakdown products, in turn, stimulate

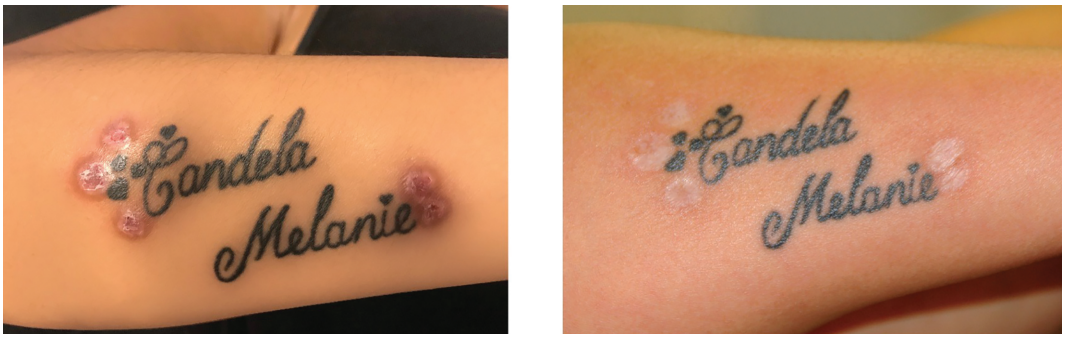

Figure 2 | Tattoo-related foreign body granulomas (left) before and (right) after three sessions of treatment with recombinant combined enzymes.

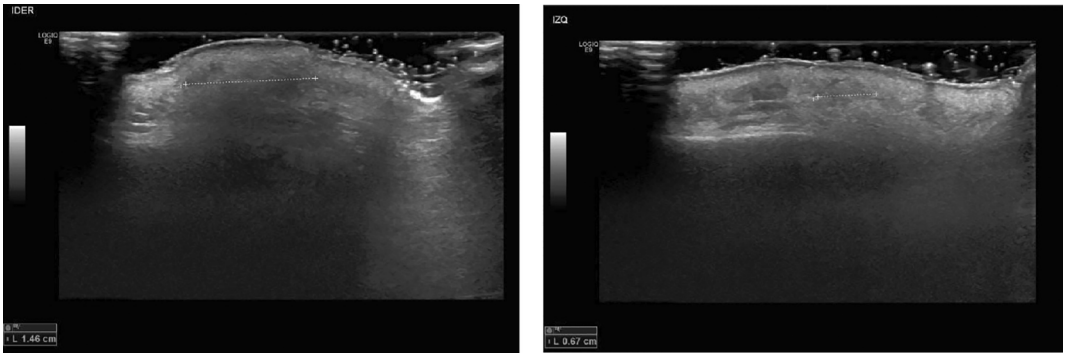

Figure 3 | (Left) Baseline ultrasonography showing an echogenic image with "snowstorm" artifacts located on the left ciliary margin (14 mm × 11 mm) before treatment; (right) reduction of the previous image (11 mm × 9.4 mm) after enzyme treatment.

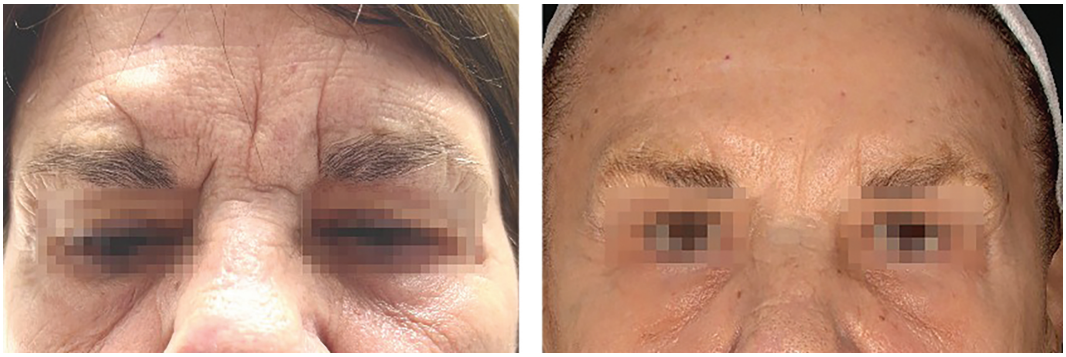

Figure 4 | Clinical changes of glabellar granuloma (left) before and (right) after enzyme treatment.

fibroblasts to produce new, functionally improved collagen fibers (5, 9). Lipase acts on locally accumulated fat, and hyaluronidase enhances tissue permeability, thereby facilitating the diffusion and action of co-administered enzymes (10).

In the cases presented here, patients were treated with a tailored protocol using this enzyme combination, with adjustments based on the degree of local inflammation. Although a high-quality pretreatment photograph was not available for Case 2, both clinical and imaging results confirmed the safety and efficacy of this novel therapeutic approach, contributing to the growing body of evidence supporting its use in foreign body granuloma management. A proposed management algorithm is presented in Figure 5 (11), which incorporates combined enzyme therapy as a viable, minimally invasive alternative to corticosteroids and surgical intervention. In addition, favorable tissue remodeling—including possible revascularization, potentially mediated by hyaluronidase (8)—was observed in histological samples. Further studies involving larger patient cohorts are needed to validate these findings.

Conclusions

Combined enzyme therapy using collagenase G/H PB220, hyaluronidase PB300, and lipase PB500 appears to be a safe and effective treatment option for foreign body granulomas. In the cases presented here, this minimally invasive approach led to significant clinical improvement, histological remodeling, and favorable tolerability. These findings support the potential role of enzyme-based therapies as a valuable alternative to traditional treatments such as corticosteroids and surgical excision. Continued research, including controlled studies with larger patient populations, is essential to further establish efficacy, optimize protocols, and define the long-term outcomes of this novel therapeutic strategy.

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Conflicts of interest

Desirée Castelanich has been a speaker for Proteos Biotech. Jorge López Berroa is the global clinical and medical head collaborator of Proteos Biotech SL. Delfina Pascuzzi has no conflicts of interest to disclose.

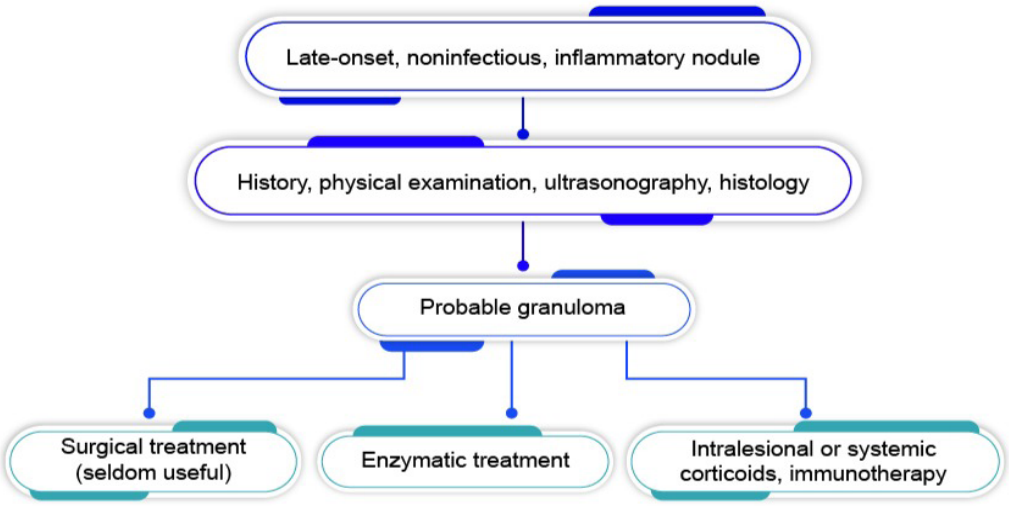

Figure 5 | Proposed algorithm for granuloma management, adapted and modified from Graivier et al. (11).

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