

Dermalive Granuloma: A Lesion With Distinctive Histological Features

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Abstract

We report the clinical and histopathological findings in two patients who had undergone treatment of facial contour abnormalities with the injectable microimplant Dermalive. Both patients presented after approximately 18 months with subcutaneous clearly palpable indurations and nodules in the area of previous augmentation. Histopathological examination of the partially excised lesions showed features of foreign body granulomas with distinctive cystic spaces. The clue to the diagnosis is the particular configuration of these cystic spaces and the characteristic shape of the foreign bodies. Dermalive granulomas show numerous round vacuoles variable in size and shape with uniform transdermal distribution. The vacuoles enclose sharply circumscribed, translucent, non-birefringent foreign bodies with variable diameter. A reactive lymphocytic infiltrate is sparse and intermingled with a few multinucleated giant cells. These histopathologic findings unequivocally allow a correct diagnosis after clinico-pathological correlation.

INTRODUCTION

Augmentation of facial tissue deficiencies and other contour abnormalities has been performed for many decades by using various materials, including organic substances such as ivory, liquid paraffin, autologous fat, and coral (^{1,2,3,4}). Inorganic substances such as liquid silicone gel have been used since the early 1960s and injectable bovine collagen since 1970 (^{5,6}). Attempts with gelatin matrix implants were performed during the last two decades (⁷). None of these treatments gave satisfactory results because of migration, host immune response, or only transitory cosmetic improvement, requiring repeated injections. With the introduction of Goretex and Artecoll a more longlasting therapy has recently become available. These are examples of permanent biologically inert implant materials. On the other hand, the market of currently used cosmetic fillers is rapidly expanding. These cosmetic fillers can be categorised in resorbable, biodegradable and (semi-) permanent (table 1). With resorbable products the tissue augmentation results from the injected volume; biodegradable products induce formation of new collagen, and permanent products cannot be eliminated. All of these cosmetic injections can give adverse reactions and face the pathologists with new and sometimes distinctive granuloma types (⁸). This side effect is mainly encountered in thin and constantly moving skin such as the face or neck (^{9,10,11}).

Figure 1

Table 1: Examples of commonly used cosmetic fillers (non-exhaustive)

Category	Commercial names	Composition
Resorbable	Zyderm, Zyplast Koken atelocollagen Restylane, Perlane Hylaform	Purified bovine dermal collagen Hyaluronic acid
Biodegradable	New-Fill	Poly-lactic acid microspheres in mannitol and carbomethoxycellulose
Permanent	Silikon 1000, Silskin Bioplastique Artecoll, Arteplast Dermalive, Dermadeep	Liquid silicone (polydimethylsiloxane) Solid silicone particles Suspended in polyvinylpyrrolidone Polymethylmethacrylate microspheres Suspended in a solution of collagen Acrylic hydrogel particles suspended in hyaluronic acid

Dermalive consists of 40% acrylic hydrogel particles, a copolymer of hydroxy-ethyl-methacrylate (HEMA) and ethyl-methacrylate (EMA), and 60% cross-linked hyaluron acid. HEMA and EMA are microspheres with a variable diameter which are nonbiodegradable and therefore ensure a longterm nature of the product. Hyaluron acid is merely a carrier substance that prevents the microspheres from agglomerating during tissue ingrowth. The carrier gel is removed within weeks and definitely replaced by a granulomatous reaction embedded within thickened collagen bundles. No over-correction, imperative in using bovine collagen, is necessary.

CASE REPORT

We describe two new patients with Dermalive-induced foreign body granulomas. On histopathology, foreign body granulomas with unusual but distinctive morphological aspects were found.

MATERIALS AND METHODS

For conventional light microscopy, formalin-fixed tissue was embedded in paraffin and stained with hematoxylin and eosin. Immunohistochemistry using antibodies against pan-T cell marker CD 3 (Dako), pan-B cell marker CD 20 (Dako) and anti-macrophage marker CD 68 (Dako) was done after heat-induced epitope-retrieval. Clinical data were obtained by review of patients' charts and by correspondence with their physician.

RESULTS

CLINICAL FINDINGS

A 58-year-old man and a 64-year-old woman presented with firm indurated nodules along the injection lines of the filler substance in the nasolabial folds and around the eyes, respectively 19 and 17 months after they were treated with Dermalive injections. Partial excision was performed in both patients. There was no relevant past medical history, in particular no symptoms of atopy, allergic reaction or autoimmune disease in both patients.

HISTOPATHOLOGICAL FINDINGS

The findings on routine histology were identical in both patients and similar to previously described Dermalive granulomas (^{8, 12}). A nodular and diffuse granulomatous infiltrate was present throughout the dermis, and extended into the underlying subcutaneous fatty tissue (Fig.1). At scanning magnification, many round, empty- looking cystic spaces, almost identical in size and shape, were observed. On higher magnification, a granulomatous infiltrate consisting of epithelioid histiocytes and few (CD 68+) multinucleate giant cells (Fig 3) was found, admixed with a sparse lymphocytic infiltrate of CD 3 positive T-cells. The cystic spaces presented as single and clustered vacuoles embedded in a sclerotic stroma. Only at highest magnification, sharply circumscribed translucent nonbirefringent foreign bodies -corresponding to the implanted methacrylate pearls- could be detected within the spaces (Fig 2).

Figure 2

Figure 1: Dermalive granuloma: A nodular and diffuse granulomatous infiltrate with numerous sharply circumscribed, apparently empty cystic spaces variable in size and shape (hematoxylin-eosin; original magnification x 50).

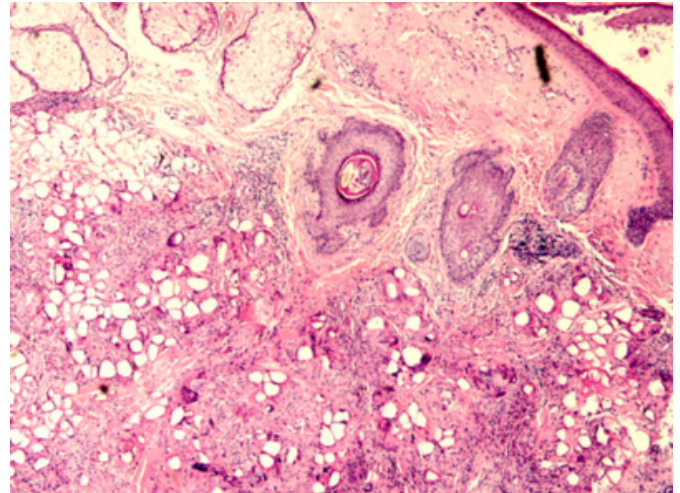


Figure 3

Figure 2: Dermalive granuloma: Higher magnification illustrates the sharply circumscribed, apparently empty cystic spaces within the multinucleated giant cells (hematoxylin-eosin; original magnification x 200).

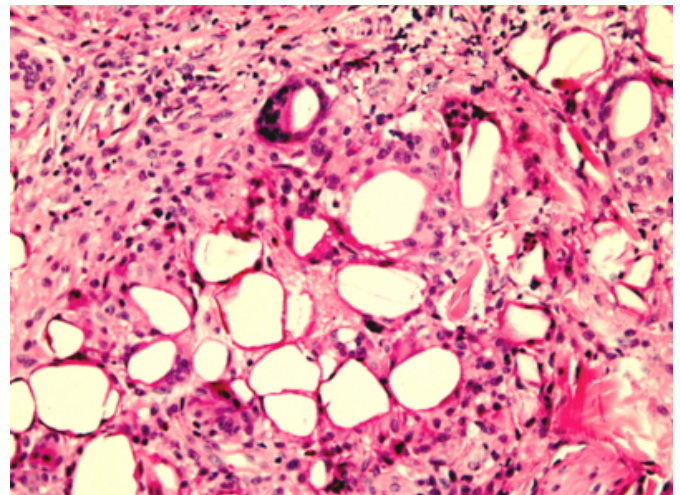
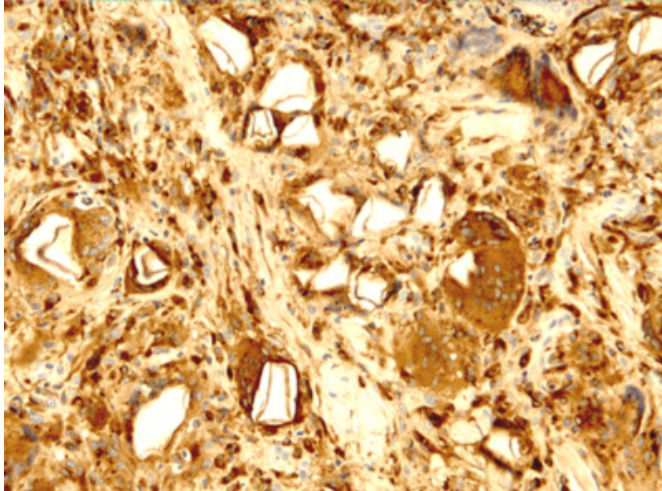


Figure 4

Figure 3: Dermalive granuloma: CD 68 positive staining of multinucleate giant cells with intracytoplasmic translucent nonbirefringent methacrylate microspheres with a variable diameter (immunohistochemistry; original magnification x 200).



DISCUSSION

Dermalive was introduced in 1998 in France and other European countries. To our knowledge, only four cases of Dermalive granuloma (^{8,13,14}) have been reported so far since 2001 (¹³), but these reports raise concern about the safety of this substance in particular and of permanent fillers in general. Because of the good cosmetic result, excision of this implant is seldom necessary. Recently we were confronted with two new cases, allowing us to study the histopathology of this inflammatory reaction in detail. We observed distinctive, identical morphological features in both patients, i.e. a granulomatous infiltrate with multinucleated giant cells surrounding evenly spaced round cystic spaces. These cystic structures contained translucent non-birefringent foreign bodies, corresponding to the implanted metacrylate pearls. The cystic spaces correspond to the outline of the pearls that presumably have separated from the granulomatous infiltrate during fixation and paraffin embedding thereby creating retraction spaces. The reactive granulomatous and lymphocytic infiltrate was rather extensive. In absence of correct clinical information, awareness of these particular morphological findings will lead to the correct histopathologic diagnosis. In that way, the clinical differential diagnosis of foreign body granuloma, allergic reaction, sarcoidosis, hypertrophic scar or keloid can be resolved with histopathologic examination.

In the histopathologic differential diagnosis, foreign body granulomas caused by other implants have to be considered,

i.e. paraffin, liquid silicone, bovine collagen, and the injectable aesthetic microimplants Bioplastique, Artecoll, New Fill and Goretex.

Paraffin was used in the very beginning of augmentation. Paraffin granulomas are still rarely seen because of the very long latency period between implantation and onset of clinical symptoms. The hallmark of paraffin granuloma is the so-called Swiss cheese pattern in the deeper dermis and subcutis. Multiple round, sharply circumscribed vacuoles of varying size are surrounded by a granulomatous reaction with multinucleated giant cells. Typically, the vacuoles are empty on high magnification.⁽¹⁵⁾

Foreign body granulomas due to injections of liquid silicone (Silikon 1000, Silskin) are characterized by geometric, angulated, translucent material within multinucleated giant cells and by round to oval vacuoles of varying size, surrounded by histiocytes, some of which may have foamy cytoplasm. Whereas the vacuoles are true liquid silicone, the angulated translucent foreign bodies represent impurities in silicone. The liquid forms of silicone are usually removed during paraffin processing resulting in an empty appearance on high magnification (^{16, 17}).

A bolus of bovine collagen in the dermis or subcutaneous fat differs from the surrounding human collagen in terms of thickness of bundles and absence of spaces between the bundles (¹⁸). The bovine collagen (commercially available as Zyderm) is mainly composed of type I collagen of relatively small fiber diameter. It can be recognized in tissues for several weeks after its injection in the form of finely fibrillar material between the larger bundles of native collagen. The granulomatous reaction surrounding the implant consists of multinucleated giant cells, lymphocytes, plasma cells and innumerable eosinophils, which can be considered to be a manifestation of hypersensitivity to bovine collagen. Bovine collagen is apparently absorbed as it can no longer be detected by light microscopy once several months have passed.⁽¹⁹⁾

Bioplastique microspheres are histologically obvious at scanning magnification and appear as jagged, translucent, non-birefringent foreign bodies that reside within bizarrely shaped, cystic structures of varying size, almost entirely enclosed by multinucleated giant cells throughout a sclerotic dermis. On the other hand, the microspheres of Artecoll granuloma are round and very smooth surfaced inducing only a mild granulomatous reaction (^{20,21}). New-Fill granuloma feature numerous giant cells including multiple

translucent particles of smaller sizes more fusiform and spiky than those of Artecoll or Dermalive. To the best of our knowledge, there is only one reported case of New-Fill granuloma in the literature (8). Gore-Tex threads seems to induce a neutrophilic reaction with extravasation of erythrocytes and formation of granulation tissue (22).

Intralesional injection of long-lasting crystalline corticosteroids has usually been the treatment of choice (23). However, this treatment bears the risk of disfigurement by skin atrophy with telangiectasis and scarring. Severe granulomas occasionally require surgical excision. Recently, patients have successfully been treated with minocycline, ciclosporine and allopurinol (9).

CONCLUSION

In conclusion, the histological diagnosis of Dermalive granuloma may be complicated if cosmetic intervention is denied or not mentioned by the patient or by the referring physician. The distinctive histopathological findings of uniformly spaced round cystic structures enclosing nonbirefringent particles must however alert dermatopathologists and allow them to make the correct diagnosis.

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