J Oral Pathol Med (2004) 33: 115–20

www.blackwellmunksgaard.com/jopm

Orofacial granulomas after injection of cosmetic fillers. Histopathologic and clinical study of 11 cases

T. Lombardi[1], J. Samson[1], F. Plantier[2], C. Husson[2], R. Küffer[1,2]

[1]*Laboratory of Histopathology, Division of Stomatology, Faculty of Medicine, University of Geneva, Switzerland, and* [2]*Laboratory of Histopathology, Department of Dermatology, Tarnier-Cochin University Hospital, Paris, France*

BACKGROUND: Purposely, cosmetic injections in orofacial tissues of various resorbable, biodegradable, or permanent fillers may be followed by development of foreign-body granulomas. The aim of this article is to contribute to the histologic identification of the filler material.
METHODS: Histologic and clinical features of 11 cases of granulomas on orofacial fillers are described.
RESULTS: Only 3/11 patients knew the nature of the injected product. Four histologic patterns were found: (i) Artecoll, (ii) Dermalive, and (iii) New-Fill granuloma, all three of the classic giant cell granuloma type, differing in respect of foreign particles; and (iv) Liquid Silicone granuloma, which featured a cystic and macrophagic type. Information was often missing or misleading, patients or practitioners being reluctant to give the details.
CONCLUSION: Increasing demand for orofacial tissue augmentation makes pathologists face new, and sometimes, puzzling granuloma types. Identification of the foreign product might be required for therapeutic or medico-legal reasons.
J Oral Pathol Med (2004) **33**: 115–20

Keywords: Artecoll; cosmetic implants; Dermalive; New-Fill; orofacial granuloma; silicone granuloma

Demand for injections of various substances in orofacial tissues has been in constant augmentation during the past 40 years (1). Mostly performed in perioral, periocular, and cheek areas of middle-aged women, it aims to smoothen out wrinkles or creases, and to produce an artificial augmentation of lip or cheek volume for cosmetic and rejuvenation purposes. More recently, injections of polylactic acid filler have been proposed to correct facial lipodystrophy occurring in AIDS patients (2). In the 1960s and 1970s, after unsuccessful attempts with various oils, the earliest injected substances were liquid silicone, and since 1981, purified bovine dermal collagen was used. Increasing demand as a result of movie-star modeling led to the development of an amazing number and variety of commercial 'cosmetic fillers', of which only a few, and not necessarily the same, have been approved either by the European Community (EC) or by the Food and Drug Administration (FDA) in USA. A non-exhaustive list is given in Table 1, excluding, for instance, human cadaver-derived and autologous products. It includes examples of the three categories of presently existing injectable fillers: resorbable products (tissue augmentation is as a result of the injected volume, maximum persistence in tissues: 4–6 months), biodegradable products (persisting for about 18 months, but inducing production and volume replacement by newly formed collagen), and permanent products (that cannot be eliminated, either supposed to be inert like silicone, or to induce formation of new collagen). Most of the new fillers seem to be well tolerated, but various adverse reactions are still possible, especially with permanent products (3). Among them, foreign-body granulomas are held by manufacturers to be rare, and not always clearly distinguished from 'nodules'. This latter term seems to be meant for little bumps appearing rapidly after the injection, as a result of an uneven distribution of product in the tissues. Histologic features of filler-induced granulomas are poorly documented, although some rather recent cases have been reported mainly in the dermatologic literature.

Materials and methods

In Table 2, 11 cases of orofacial foreign-body granulomas, developed after injection of various cosmetic fillers, have been summarized. All the patients were women, with a mean age of 55 years. Ten cases consisted primarily in submitted biopsy specimens, and in 6 cases, the patients were clinically examined or operated by two of us. In 10 patients, we examined at least 1 incisional or excisional biopsy, including case 3 in which 3 excisional biopsies were obtained. A total of 12 biopsy specimens had been taken from lips (upper 3, lower 2, commissure 1), cheeks (2), nasolabial grooves (1), glabella (2), and lower eyelid (1). They were submitted with a clinical diagnosis of suspected 'granuloma on injected filler' in five patients and of 'nodule' or 'salivary cyst' in four patients. In one case, the lesion was fortuitously discovered

Correspondence: Dr T. Lombardi Laboratory of Histopathology, Division of Stomatology, 19 rue Barthélémy-Menn, 1211 Geneva 4, Switzerland. E-mail: Tommaso.Lombardi@medecine.unige.ch
Accepted for publication April 1, 2003

Table 1 Examples of main currently used cosmetic fillers (non-exhaustive)

Category	*Commercial names*	*Composition*	*Approval*[*]	
			FDA	*EC*
Resorbable	Zyderm, Zyplast Koken atelocollagen	Purified bovine dermal collagen	Yes	Yes
	Restylane, Perlane, Hylaform	Hyaluronic acid	Yes	Yes
Biodegradable	New-Fill	Polylactic acid microspheres in mannitol and carbomethoxycellulose	No	Yes
Permanent	MDX 4–4011 Dow Corning Silikon 1000, Silskin	'Medical-grade silicone oil' Liquid silicone (polydimethylsiloxane)	No	No
	Bioplastique	Solid silicone particles suspended in polyvinylpyrrolidone	No	Yes
	Artecoll, Arteplast	Polymethylmethacrylate microspheres suspended in a solution of collagen	No	Yes
	Dermalive, Dermadeep	Acrylic hydrogel particles suspended in hyaluronic acid	No	Yes

[*]November 2002.
FDA, Food and Drug Administration; EC, European Community.

Table 2 Granulomas induced by aesthetic fillers

Case	*Gender and age (years)*	*Site(s) of lesion(s)*	*Clinical symptoms*	*Clinical aspect*	*Patient's data before biopsy*	*Clinical diagnosis before biopsy*	*Patient's data after biopsy*	*Data from practitioner*	*Delay between injection and granuloma*	*Histological diagnosis*[*]
1	F 51	Cheek	None	Interstitial nodule	None	Interstitial nodule	Injections of 'collagen'	Injected product was Arteplast	'Years'	CFBG type 1 (Arteplast)
2	F 53	Glabella	Slight pain edema	Inflammatory infiltration	Injection of Artecoll	Granuloma on Artecoll	None	Not joined	3 years	CFBG type 1 (Artecoll)
3	F 58	Upper lip Commissure Cheeks Glabella	Discomfort	Multiple bulging and interstitial nodules	'Multiple injections of Dermalive' other fillers?	Granulomas on an unknown injected filler	None	Not joined	'About 1 year after last injections'?	Association of: CFBG type 1 CFBG type 2 CMG
4	F 51	Lower lip	None	Submucous nodule	None	Salivary cyst	Injections of unknown filler	None	Unknown	CFBG type 2 (Dermalive)
5	F 42	Nasolabial grooves	Discomfort	Bulging stiff infiltration	Injection of unknown fillers	Granuloma on injected filler	'New-Fill'? unknown filler 7 years before	Not joined	'6 months' after last injection	CFBG type 3 (New-Fill)
6	F 52	Cheeks nasolabial grooves	Discomfort transitory edema	Submucous interstitial nodules	'Injection of Dermalive' other fillers?	Granuloma on Dermalive or other filler	None	Not joined	'3 years after last injection'	CMG (silicone)
7	F 57	Glabella	None	Superficial nodules	None	Granuloma on injected filler	Lost of view	None	Unknown	CMG
8	F 64	Lower eyelid	None	Clinically latent, below a carcinoma	None	Basal cell carcinoma (undiagnosed granuloma)	None	Not joined	Unknown	CMG
9	F 46	Lower lip	Discomfort edema	Submucous nodule	None	Lip nodule	Injections of 'collagen' other filler?	Injected Koken atelocollagen other filler?	'2 years after last injection'	CMG
10	F 81	Upper lip	None	Nodules	None	Lip nodules	None	Bovine collagen other filler?	'6 years after last injection'	CMG
11	F 50	Upper lip	None	Persistent lip augment. and nodules	Injections of Restylane and collagen	Granuloma on Restylane?	None	Restylane, 7 years after Zyderm/Zyplast	'About 6 months after Restylane'	(–)

[*]CFBG: classic foreign body type granuloma; CMG: cystic and macrophagic-type granuloma.

in a biopsy specimen. In each case, we tried to obtain additional information from the patient or the clinician who performed the biopsy, and when possible, from the practitioner who had injected the filler.

Results

The lesions were mostly asymptomatic. There was slight pain or mild discomfort in 5/11 cases, with transient facial

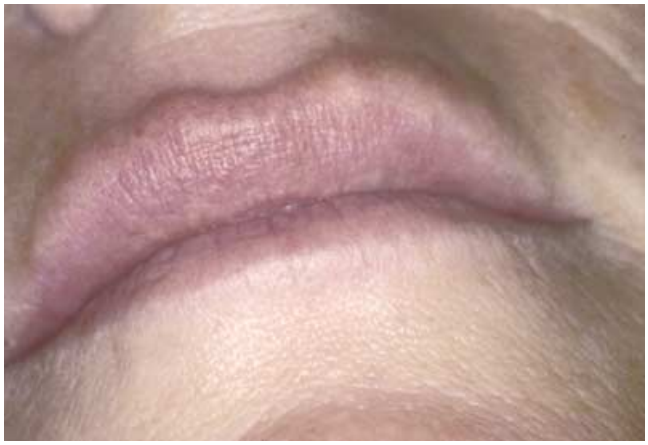

Figure 1 Persistent upper lip augmentation with some lately appeared small firm nodules set in line along the muco-cutaneous border of the upper lip, 2 years after injection of Restylane (case 11).

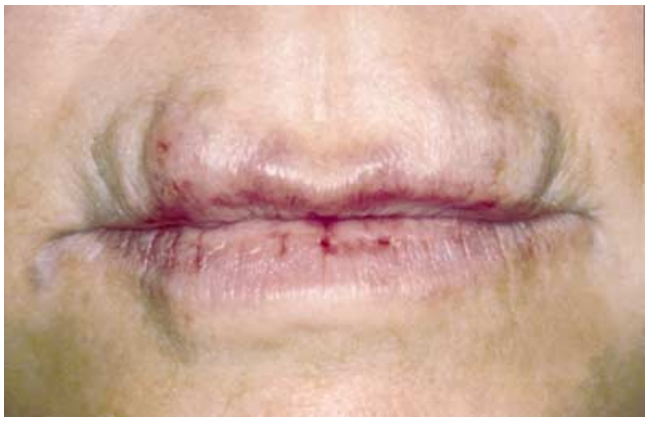

Figure 2 Clinical aspect of the lips about 1 year after the last of the multiple injections of Artecoll, Dermalive, and liquid silicone was given: bulging nodules of the right commissure, upper lip, and right side of lower lip (case 3).

edema in 3/11 cases. The lesion was not clinically visible in 1/11 case, and more or less large nodules bulging under the skin or lip vermilion motivated the consultation in 4/11 cases. In spite of some small nodules, which had appeared lately, 1/11 patient was satisfied with the abnormal 2 years of long persistence of her lip augmentation (usually 6 months), suggesting the presence of granulomas, and she refused biopsy (Fig. 1).

Almost every section of the 12 biopsy specimens from 10 patients showed a poorly limited foreign-body granuloma, either superficial in the facial or labial dermis, or more deeply situated in the hypodermis. Some granulomas extended through the muscle from the dermis to the submucosa of the lip or cheek. We have identified two main types of granulomas: the classic foreign-body granuloma type (CFBG), featuring numerous giant cells around the foreign bodies, and the cystic and macrophagic granuloma type (CMG), characterized by extracellular microcysts surrounded by a mainly mononuclear infiltrate of vacuolated macrophages. In our patients, three patterns of CFBG could be distinguished, differing mainly in the microscopical aspect of the foreign body particles, each pattern corresponding to a particular filler or category of fillers: type 1 for Artecoll or Arteplast, type 2 for Dermalive, type 3 for New-Fill granulomas. In the CMG-type corresponding to Liquid silicone granuloma, there were slight differences consisting mainly in the more or less obvious presence of giant cells. Every patient presented one type, except patient 3 (Fig. 2), in whom contiguous sites of the upper lip and commissure featured a various mixture of three different types, CFBG 1, CFBG 2, and CMG, showing that at least three different fillers had been injected one after another in the same or in the adjoining areas. A legal action had been taken by the patient, and the responsible practitioners could not be joined.

Comments

Artecoll granuloma (cases 1–3) featured a CFBG type 1 granuloma around multiple small round cystic spaces of approximately the same size, included in the cytoplasm of large foreign-body-type giant cells, or adjacent to giant cells often containing asteroid bodies or clusters of tiny clear vacuoles (Fig. 3). Apparently empty at first sight, these spaces contained a translucent round microsphere, non-birefringent in polarized light (Fig. 3, inset). They were rather unevenly distributed on a background of collagen fibrosis, with a variable infiltrate of lymphocytes. According to the practitioner, in case 1, the filler was Arteplast, an earlier version that could not be microscopically distinguished from Artecoll. Introduced in Europe in 1991, it was made of slightly smaller acrylic microspheres suspended in gelatine. Because of electrostatic forces, they retained on their surface a dust of acrylic particles that favored the development of foreign-body granulomas in 3–5% of the cases. In Artecoll, introduced in 1995, this dust was removed by repeated washings, reducing to less than 0.01%, the incidence of granuloma formation (4). Only seven cases of granulomas on more than 100 000 Artecoll injections were reported until 1999, and since then, six other cases have been added (5, 6).

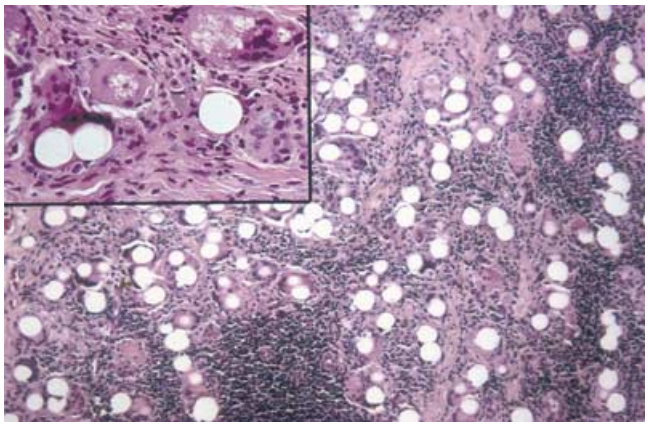

Figure 3 Arteplast granuloma: CFBG type 1, with small round apparently empty cyst-like spaces, all of approximately the same size (case 1, H&E ×25). Inset: Artecoll granuloma: same aspect of CFBG type 1 granuloma; the cystic spaces contain a round translucent and non-birefringent microsphere (case 3, H&E ×100).

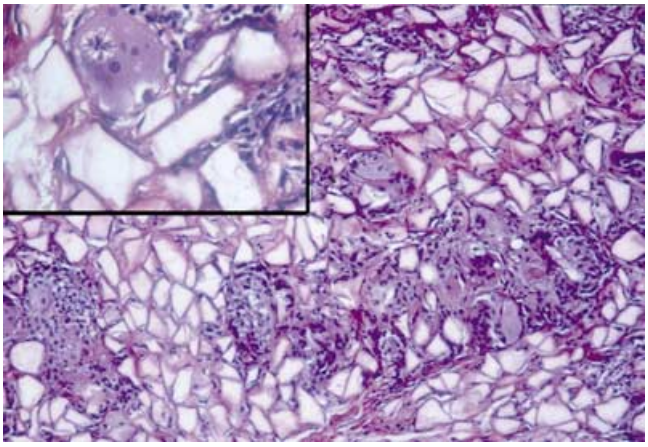

Figure 4 Dermalive granuloma: CFBG type 2 granuloma, with clusters of small pinkish polygonal particles, translucent and non-birefringent, of irregular shape and size (case 3, H&E ×25). Inset: giant cell with asteroid body (case 4, H&E ×100).

Dermalive granuloma (cases 3 and 4) featured a CFBG type 2 granuloma, including multiple small translucent pinkish particles of slightly different sizes, polygonal or irregularly shaped, non-birefringent, unevenly distributed on a background of finely fibrillar collagen with a variable lymphocytic infiltrate (Fig. 4). Giant cells, some of them containing asteroid bodies (Fig. 4, inset), formed islands in a more patchy distribution among the closely packed particles than in the preceding type. Dermalive was introduced in 1998 in France and other European countries. To our knowledge, only two cases of Dermalive granuloma (7, 8) have been reported so far.

New-Fill granuloma (case 5) featured a CFBG type 3 granuloma, with numerous giant cells including multiple translucent particles of different sizes (smaller) and some of them more fusiform or spiky than those of Artecoll, with which they could, at first sight, be confused (Fig. 5, left), but they were birefringent in polarized light (Fig. 5, right). Some giant cells contained asteroid bodies, and the well-limited granulomatous patches were sprinkled by a mild lymphocytic infiltrate. To the best of our knowledge, this case is the first to be reported in the literature. New-Fill is a biodegradable and bioresorbable filler composed of polylactic acid (PLA) microspheres suspended in a mannitol and carbomethoxycellulose solution, which was created and admitted in Europe in 1999. It has since gained a reputation of a very safe and reliable product, as PLA had already been utilized for years in resorbable surgical material, such as sutures, plates, and screws for bone tissues, and membranes for guided-tissue regeneration in periodontal surgery (9). The immediate tissue augmentation after injection of New-Fill is purely mechanical. The carrier solution is rapidly resorbed, and then a slow process of biodegradation of microspheres takes place. It consists of hydratation, loss of cohesion and molecular weight, solubilization and phagocytosis of PLA by the host's macrophages (10), synchronously associated with a PLA-induced synthesis of collagen, which is aimed to produce the cosmetic result. This process is estimated to go, on an average, for 10–12 months, with extremes of 7 months to 2 years. In our case, it seems to have been protracted far beyond the normal range for some reason, perhaps because of injection of an unknown filler in the same place 7 years ago. Biodegradation explains the small size and irregular shape of particles, which could no longer be called microspheres, and allows hoping that things will spontaneously return to normal in a more or less near future.

Liquid Silicone granuloma, our most frequent histologic finding (cases 3 and 6–10) was of the CMG type, featuring, at low magnification, a particular pattern of round holes of different sizes, sometimes confluent, on a background of more or less foamy infiltrate. This 'Swiss cheese pattern' was made of extracellular microcysts with an empty cavity rimmed by a thin layer of collagen (Fig. 6), and of a surrounding clear cell infiltrate composed of a variable mixture of vacuolated macrophages and giant cells. Microcysts and vacuoles appeared empty because silicone oil had been completely eliminated through laboratory processing. Giant cells were completely lacking in cases 7 (Fig. 7, left) and 8, rather rare in cases 3, 9, and 10, and more numerous in case 6 in which they took a daisy-like aspect (Fig. 7, right) – numerous clear peripheral vacuoles surrounding a central

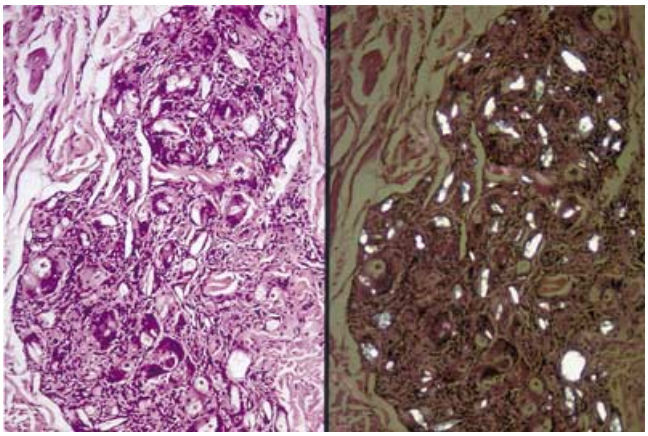

Figure 5 New-Fill granuloma: CFBG type 3 granuloma, with numerous translucent particles of irregular shape and size, some very small and spiky (case 5). Left: H&E staining (H&E ×25); right: same field in polarized light, foreign body particles are birefringent.

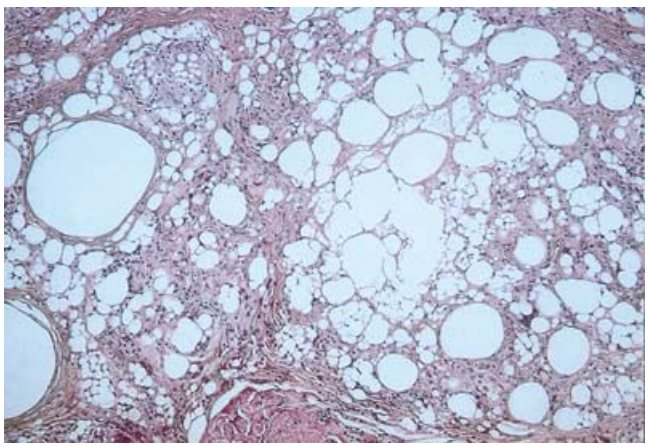

Figure 6 Liquid silicone granuloma: at low magnification, CMG showing a typical 'Swiss cheese pattern' of particularly numerous empty round extracellular microcysts of different sizes (case 6, H&E ×20).

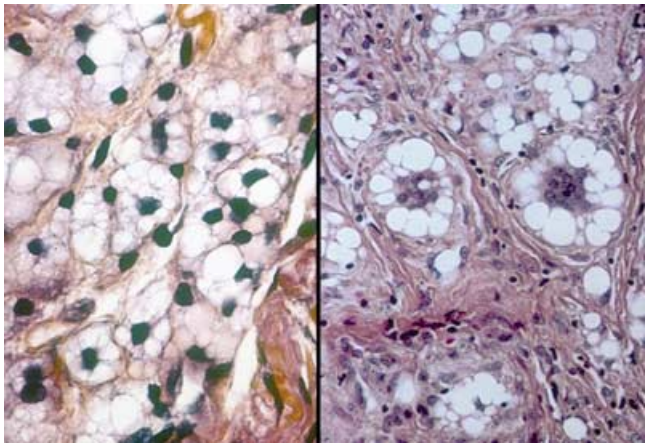

Figure 7 Liquid silicone granuloma. Left: high magnification of the CMG, showing the background of mononuclear macrophages, containing one or several clear vacuoles (case 7, H&E ×100); right: background of macrophages, with daisy-like vacuolated giant cells (case 6, H&E ×50).

cytoplasmic residue filled with closely cropped nuclei. In all cases, the mononuclear macrophages were massively vacuolated, some cells being apparently reduced to tiny holes in the tissue, with sometimes a notched nucleus cornered between contiguous vacuoles. There was always a variable amount of lymphocytic infiltrate and peripheral fibrosis. This CMG pattern was so different from the CFBG type that some authors considered it to be a non-granulomatous macrophagic reaction (11). These authors thought that injectable pure medical-grade silicone oil extensively used in USA was an inert substance that could not initiate granulomas: foreign-body granulomas were attributed to the use of non-medical grade, or of silicone oil voluntarily adulterated with various products like olive oil. This procedure was meant to 'fix' silicone droplets in the tissues and prevent them to migrate to distant sites and viscera (11, 12), a frequent and occasionally dangerous drawback of liquid silicone. The notion of a fully safe inert implantable material was, however, criticized (13), and cases of silicone granulomas in which adulteration of the filler could not be suspected were reported (14, 15). Liquid silicone is not approved for tissue augmentation by EC and FDA, but used illegally in many European and American countries with products of various origin and uncertain grade and purity. This fact might explain certain slight differences in histologic aspect in our cases, as well as in other recently published reports (7, 8, 16–19), especially in the six cases of Rodriguez de Valentiner et al. (20), who distinguished three variants ('xanthelasmized', 'Swiss cheese', and 'inflammatory').

Liquid silicone granuloma should not be confused with the granulomatous reaction induced by solid silicone (elastomer), which is of the CFBG type. It is especially the case with Bioplastique, injectable filler containing solid silicone particles used in European countries; at least four cases of Bioplastique granuloma have been reported and described as CFBG with small cystic spaces of varying shape and size containing jagged, translucent, non-birefringent foreign bodies (5, 6, 8). This pattern could be added to our list as CFBG type 4 granulomas (Table 3).

Patient 11, who refused biopsy, raised the problem of a possible granulomatous reaction to bovine collagen (Zyderm), or more probably to Restylane, a non-animal hyaluronic acid filler derived from bacterial cultures. Adverse effects of CFBG type seem to be rare, but have been reported to both Zyderm (21, 22) and Restylane (23, 24), and estimated more frequently in patients sensitized to these products, although they can also occur in non-sensitized patients. Skin testing showed that patient 11 was not sensitized to these two fillers.

The clinical diagnosis of orofacial granulomas can be difficult when patients are not aware of the relation with injections of filler(s), sometimes made many years ago, or if they deliberately omit to mention them when consulting for progressively developing nodules or facial swellings. The lesions can be misdiagnosed as cysts, tumors, or other chronic diseases (19). Experience shows that patients rarely know the name or nature of the filler material, and that the practitioner who injected the product might no longer be joined, or be reluctant to give details. Histologic examination is the best means to obtain the correct diagnosis of foreign-body granuloma, and in case of permanent material, to identify the type of filler particles.

Our case of New-Fill granuloma might have been discussed with a silicotic granuloma. This latter lesion often results from a past accidental inclusion of soil particles in a wound, in which case the granulomatous reaction around birefringent crystals is embedded in scar tissue (15, 25–27).

Table 3 Histologic aspect of injectable filler granulomas

Type	*Common features*	*Subtype*	*Aspect of foreign body*	*Aesthetic filler*
CFBG (classic foreign-body granuloma)	Predominant giant cells engulfing foreign bodies	Type 1	Multiple small round cystic spaces containing translucent non-birefringent microspheres of approximately same size	Artecoll (or arteplast)
	Asteroid bodies	Type 2	Clusters of small translucent pinkish polygonal particles, of irregular size and shape	Dermalive
	Fibrosis	Type 3	Multiple small translucent and birefringent particles of different size and shape, some of them more or less spiky	New-Fill
	Lymphocytic infiltrate	Type 4	small cystic spaces of varying shape and size containing jagged, translucent, non-birefringent foreign bodies (5, 6)	Bioplastique
CMG (cystic and macrophagic granuloma)	More or less numerous extracellular microcysts on a background of mainly mononuclear vacuolated macrophages		As liquid silicone is dissolved and eliminated during histologic slide processing, microcysts and vacuoles in macrophages cytoplasm seem to be empty	Liquid silicone

A more rare possibility is the accidental inclusion of silica or silicate-containing dental products in oral tissues during dental care (28).

The clear vacuolated macrophages of Liquid silicone granuloma in case of scarce microcysts might be overlooked and easily mistaken as adipocytes, and at casual examination, the lesion might be misdiagnosed as sclerosing lipogranuloma (11).

Conclusion

Oral pathologists might encounter, in a near future, an increasing number of bizarre orofacial foreign-body granulomas. When proper information is lacking among various hypotheses, a possible injection of one or more cosmetic filler products should be considered, especially among middle-aged women. When permanent fillers were injected in a large number of cases, the morphologic aspect of the foreign particles allowed to identify the injected product or category of the product. A histopathologic advice may be required if the patient takes a legal action.

References

1. Ellis DA, Makdessian AS, Brown DJ. Survey of future injectables. *Facial Plast Surg Clin North Am* 2001; **9**: 405–11.
2. Cheonis N. New Fill to treat facial wasting. *BETA* 2002; **15**: 10–5.
3. Maas CS, Papel ID, Greene D, Stoker DA. Complications of injectable synthetic polymers in facial augmentation. *Dermatol Surg* 1997; **23**: 871–7.
4. Lemperle G. Artecoll: indications, techniques and potential side-effects. 20th Congress of Dermatology 2002, Paris. *Ann Dermatol Venereol* 2002; **129**: 1S84.
5. Rudolph CM, Soyer HP, Schuller-Petrovic S, Kerl H. Foreign-body granulomas due to injectable aesthetic microimplants. *Am J Surg Pathol* 1999; **23**: 113–7.
6. Hoffmann C, Schuller-Petrovic S, Soyer HP, Kerl H. Adverse reactions after cosmetic lip augmentation with permanent biologically inert implant materials. *J Am Acad Dermatol* 1999; **40**: 100–2.
7. Requena C, Izquierdo MJ, Navarro M, et al. Adverse reactions to injectable aesthetic microimplants. *Am J Dermatopathol* 2001; **23**: 197–202.
8. Casas J, Charas V, Diaz M, et al. Cutaneous complications in facial soft tissue augmentation. 20th Congress of Dermatology 2002, Paris. *Ann Dermatol Venereol* 2002; **129**: 1S451.
9. Robert P, Mauduit J, Frank RM, Vert M. Biocompatibility and resorbability of a polylactic acid membrane for periodontal-guided tissue regeneration. *Biomaterials* 1993; **14**: 353–8.
10. Kronenthal RL. Biodegradable polymers in medicine and surgery. *Polym Sci Technol* 1975; **8**: 120–37.
11. Morgan AM. Localized reactions to injected therapeutic materials. Part 2. Surgical agents. *J Cutan Pathol* 1995; **22**: 289–303.
12. Clark DP, Hanke CW, Swanson NA. Dermal implants: safety of products injected for soft tissue augmentation. *J Am Acad Dermatol* 1989; **21**: 992–8.
13. Faure M. Complications des implants de silicone et autres matériaux dits inertes. *Ann Dermatol Venereol* 1995; **122**: 455–9.
14. Milojevic B. Complications after silicone injection therapy in aesthetic plastic surgery. *Aesthetic Plast Surg* 1982; **6**: 203–6.
15. Wilkie TF. Late development of granuloma after liquid silicone injections. *Plast Reconstr Surg* 1977; **60**: 179–88.
16. Rapaport MJ, Vinnik C, Zarem H. Injectable silicone: cause of facial nodules, cellulitis, ulceration, and migration. *Aesthetic Plast Surg* 1996; **20**: 267–76.
17. Amemiya T, Dake Y. Granuloma after augmentation of the eyelids with liquid silicone: an electron microscopic study. *Ophthal Plast Reconstr Surg* 1994; **10**: 51–6.
18. Pimentel L, Barnadas M, Vidal D, Sancho F, Fontarnau R, Alomar A. Simultaneous presentation of silicone and silica granuloma. A case report. *Dermatology* 2002; **205**: 162–5.
19. Ficarra G, Mosqueda-Taylor A, Carlos R. Silicone granuloma of the facial tissues: a report of seven cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **94**: 65–73.
20. Rodriguez de Valentiner AR, Lopez C, Lopez R, Chopite M, Ramirez R, Oliver M. Histopathologic characteristics of cutaneous lesions caused in dermal implants. 20th Congress of Dermatology 2002, Paris. *Ann Dermatol Venereol* 2002; **129**: 1S486.
21. Heise H, Zimmermann R, Heise P. Temporary granulomatous inflammation following collagen implantation. *J Craniomaxillofac Surg* 2001; **29**: 238–41.
22. Garcia-Domingo MI, Alijotas-Reig J, Cistero-Bahima A, Tresserra F, Enrique EJ. Disseminated and recurrent sarcoid-like granulomatous panniculitis due to bovine collagen injection. *Invest Allergol Clin Immunol* 2000; **10**: 107–9.
23. Friedman PM, Mafong EA, Kauvar AN, Geronemus RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg* 2002; **28**: 491–4.
24. Lowe NJ, Maxwell CA, Lowe P, Duick MG, Shah K. Hyaluronic acid skin fillers: adverse reactions and skin testing. *J Am Acad Dermatol* 2001; **45**: 930–3.
25. Hannon SM, Picket AB, Frost JM. Foreign body (silica) granuloma of the lip. *J Oral Maxillofac Surg* 1983; **41**: 470–2.
26. Harms M, Masouye I, Saurat JH. Silica granuloma mimicking granulomatous cheilitis. *Dermatologica* 1990; **181**: 246–7.
27. Mowry RG, Sams WR Jr, Caufield JB. Cutaneous silica granuloma. A rare entity or rarely diagnosed? Report of two cases with review of the literature. *Arch Dermatol* 1991; **127**: 692–4.
28. Lombardi T, Kuffer R, Dubrez B. Polishing paste-induced silica granuloma of the gingiva. *Dermatology*, 2001; **203**: 177–9.

Acknowledgements

We thank Dr P. Bui Quy Minh for providing case 2, Dr I. Masouyé for providing sections of case 6, and Dr F. Lepelletier for providing sections of case 10.