

Lipogranuloma after facial cosmetic procedures



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Objective. Lipogranuloma is a rare inflammatory reactive process in the dermis and subcutis. We present a summary of the 6 cases of lipogranuloma after facial cosmetic procedures.

Study Design. We performed a retrospective review including patient demographic data, clinical symptoms, appearance on computed tomography, treatment, pathology results, and history of facial cosmetic procedures.

Results. In most cases, the nodules were painless and showed no significant growth. Computed tomography revealed ill-defined swellings in the buccal fat pad with heterogeneous density. Histopathological examinations revealed numerous variable-sized empty microcysts surrounded by abundant lymphocytes and foamy macrophages, the characteristic features of lipogranuloma. On further questioning, all of the patients revealed that they had undergone some form of facial cosmetic procedure in the preceding months to years. Among the 6 cases, facial autologous fat injection may have been the main cause of lipogranuloma.

Conclusion. Lipogranulomas can develop months to years after facial cosmetic procedures distant from the injection sites. A thorough understanding of the patient's medical history and the clinical and histopathologic characteristics of lipogranuloma are necessary to make a definite diagnosis and allow appropriate treatment. (*Oral Surg Oral Med Oral Pathol Oral Radiol* 2017;123:e123-e132)

Lipogranuloma is a rare reactive inflammatory process in the dermis and subcutis that typically manifests clinically as subcutaneous nodules or rubbery lymphadenopathy.^{1,2} Two mechanisms have been proposed for the development of lipogranuloma. The first is a foreign-body reaction to an exogenous lipid/oil-like substance such as paraffin or silicone.^{1,3} The second is a granulomatous reaction caused by endogenous degeneration of lipids secondary to infection, trauma, extremes of temperature, or allergic reaction.⁴ Reports of lipogranuloma in the orofacial region are relatively few, and mainly limited to the periorbital area. **Table I** presents a brief summary of these cases.^{3,5-27}

In the last 4 years, we encountered several patients with similar symptoms and pathologic characteristics. All were middle-aged women who reported nodules in the orofacial region; however, their medical histories seemed unremarkable at their first visits and the etiology of their nodules was unknown. All underwent surgical removal of the nodules in our hospital. Histopathological examinations of the resected nodules revealed characteristic features of lipogranuloma,

namely numerous empty microcysts of differing sizes and shapes, surrounded by abundant lymphocytes and foamy macrophages. Even after being informed that their pathology results revealed a reaction to a foreign body, the patients continued to deny a history of trauma or any past experience that may have predisposed them to the condition. During follow-up, the clinicians continued to remind the patients of the importance of medical history in making a correct diagnosis. Eventually, each patient admitted undergoing some form of facial cosmetic procedure in the preceding months to years.

We describe 6 cases of lipogranuloma that developed after facial cosmetic procedures and provide information that may be helpful for oral and maxillofacial clinicians who encounter this rare condition.

MATERIALS AND METHODS

We reviewed the reports of all pathologic examinations performed over a 4-year period, from 2013 to 2016, at the Department of Oral Pathology, Peking University School and Hospital of Stomatology, and identified 6 that had the typical features of lipogranuloma; all 6 histopathological reports were descriptive and identified features such as microcysts, chronic inflammation, fat

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Statement of Clinical Relevance

Lipogranuloma is a rare complication after facial cosmetic procedures that is seldom recognized by oral and maxillofacial clinicians. We summarize the characteristics of lipogranuloma, which may be helpful for clinicians who encounter similar conditions.

necrosis, and foreign-body reaction. We contacted the patients and asked them to come for a follow-up visit, during which we elicited a detailed history. We performed a retrospective review, including demographic data, clinical symptoms, computed tomography (CT) appearance, treatment, pathology results, and history of facial cosmetic procedures. All of the patients signed informed consent for this review. The study was approved by the Ethics Committee of the Stomatological Hospital of Peking University (PKUSSIRB-201627037).

RESULTS

The clinical characteristics of the 6 patients with lipogranuloma are summarized in Table II. They were all women, with a mean age of 39.8 years (range 27-50). They had visited the hospital complaining chiefly of nodules in the orofacial region for 3 to 6 months. In most cases, these nodules were painless and palpable, with no significant growth over several months. Three of the patients had more than one nodule. At their first visit, they all denied any predisposing causes that could have been related to the nodules, such as trauma, infection, or surgery.

Four patients underwent CT scans. The nodules were found in the buccal fat pad and were ill-defined and heterogeneous in density (Figure 1). In all cases, the nodules were excised and sent for histopathological examination. Hematoxylin and eosin-stained sections revealed numerous variable-sized empty microcysts, some of which were rimmed by a thin layer of eosinophilic crenulated material, which has been described as a "Swiss cheese" pattern. Abundant lymphocytes and foamy macrophages infiltrated the surrounding adipose tissue and fibrous tissue, characteristic of chronic inflammatory reaction in the soft tissues (Figure 2). The histopathological manifestations of the six patients were similar (Supplementary Figures 1-6). These features were consistent with a diagnosis of lipogranuloma.

During follow-up, detailed questioning about each patient's medical history was performed. Eventually, all patients admitted to having undergone a facial cosmetic procedure in the past. Facial autologous fat injection was performed in 4 patients, 2 of whom also received injection of botulinum toxin. The other 2 patients had undergone injection of both botulinum toxin and hyaluronic acid. Patient 5 had also undergone rhinoplasty and was the only one to have received plastic surgery.

DISCUSSION

Over the last several decades, facial cosmetic procedures have continued to gain in popularity.²⁸ Although most cosmetic procedures are reported to be well tolerated, the numbers of complications are increasing as more procedures are performed. In patients who

are reluctant to admit they have undergone cosmetic procedures, the diagnosis can be clinically challenging. Diagnostic difficulties in these 6 cases can be attributed to 3 factors: the accuracy of patient-provided history of cosmetic procedures, the type of cosmetic procedure used, and the migration of the lipogranuloma.

The first factor that complicated diagnosis in our 6 cases was the patients' concealment of their history of cosmetic treatments, so the clinicians did not initially realize that there was a relationship between the nodules and prior procedures. The clinical presentations of lipogranuloma lack specificity; therefore, clinicians cannot make a definite diagnosis based on physical examination or CT manifestations. The pathology reports contained descriptions of microcysts, inflammation, and fat necrosis. Because some oral pathologists are unfamiliar with the histopathological characteristics of lipogranuloma, the diagnosis may have been missed. Hence, the patients were often misdiagnosed at other hospitals as having cysts, mucoepidermoid carcinoma, or parasitic infection.

Histopathologically, lipogranuloma should be differentiated from extravasation mucocoeles. The most frequent site of a mucocoele is the lower lip, followed by the buccal mucosa. Occasional patients have multiple mucocoeles. Microscopy shows ill-defined pools of mucus. The pools eventually become surrounded by fibrosis and compressed macrophages, many of which contain abundant mucus; similar cells can be seen floating freely in the cyst cavity.²⁹ A lipogranuloma, on the other hand, never contains mucus. Low-grade mucoepidermoid carcinoma can also resemble lipogranuloma. Slightly more than half of mucoepidermoid carcinomas arise in the major salivary glands, with the parotid gland being the most frequent site involved.²⁹ Bilateral lesions are rare. These low-grade tumors are characteristically composed of multiple variably sized cystic structures that are lined predominantly by mucous cells. Solid nests are a minor component and are composed mainly of intermediate cells. Squamous cell differentiation and clear-cell change may be present.²⁹ Identification of neoplastic epithelial and mucous cells will help exclude the possibility of lipogranuloma. Oral cysticercosis, a rare parasitic infestation, can also be confused with lipogranuloma. Histopathological examination of an excisional biopsy specimen will reveal a cystic cavity lined with a digitiform layer of homogenous eosinophilic material, which could be confused with the picture seen in lipogranuloma of microcysts rimmed by a thin layer of eosinophilic crenulated material. To make a definitive histologic diagnosis of cysticercosis, it is necessary to visualize the parasite. The live parasite has a single scolex, with 4

Table 1. Summary of reported cases of lipogranulomas in the orofacial region

<i>First author</i>	<i>Cases</i>	<i>Locations</i>	<i>Cause</i>	<i>Clinical characteristics</i>	<i>Radiographic characteristics</i>	<i>Histopathological characteristics</i>	<i>Differential diagnosis</i>
Witschel, 1994 ⁵	10	Eyelids and anterior orbit	Endonasal sinus surgery	Swelling, ptosis	Diffuse infiltration of the lid tissue, sometimes including the anterior orbit (CT)	Microcysts, foreign-body reaction, inflammation, foam cells	Not given
Shigetaka, 1996 ⁶	1	Parotid region	Leakage of lipid contrast medium after sialography	Swelling, trismus, erythema	Soft mass lesion containing radiopaque areas (CT)	Microcysts, foreign-body reaction, chronic inflammation, fibrosis	Not given
Robenzadeh, 1998 ⁷	1	Perioral area	Injection of vitamin E to perioral area	Swelling, tenderness, erythema	Not given	Microcysts	Cellulitis
Bigata, 2001 ⁸	1	Lips and nasolabial folds	Injections of liquid silicone to lip	Swelling	Not given	Microcysts	Facial inflammation, granulomatous reactions
Ficarra, 2002 ⁹	7	Lips	Injection of liquid form of silicone to lips	Swelling, redness, pain	Not given	Microcysts, fibrosis, foreign-body reaction; did not stain with PAS, Alcian blue, or Oil Red O	Melkersson Rosenthal syndrome, labial salivary gland adenoma, etc.
Bassichis, 2003 ¹⁰	1	Nasal dorsum	Endoscopic sinus surgery and rhinoplasty with ointment as nasal packing	Widened nasal dorsum	Not given	Microcysts, foreign-body reaction	Not given
Abel, 2003 ¹¹	1	Upper eyelid	Periocular injection of corticosteroids	Erythema, ptosis of the upper eyelid	Large mass in the superior orbit with a “tail” laterally extending toward the globe (CT)	Microcysts, foreign-body reaction, inflammation	Sarcoidosis or Wegener’s granulomatosis
Salmi, 2004 ¹²	1	Cheeks	Injection of liquid silicone to the face	Swelling	Not given	Foreign-body reaction, granulomatous, inflammation	Not given
Maly, 2004 ¹³	1	Upper lip	Injection of liquid silicone to upper lip	Swelling	Not given	Microcysts, positive staining with anti-CD-68 and anti-lysozyme antibodies	Liposarcoma

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Table I. Continued

<i>First author</i>	<i>Cases</i>	<i>Locations</i>	<i>Cause</i>	<i>Clinical characteristics</i>	<i>Radiographic characteristics</i>	<i>Histopathological characteristics</i>	<i>Differential diagnosis</i>
Arin, 2005 ¹⁴	1	Left eye, upper lip, nose	Injection of silicone to nose	Swelling, erythema	Not given	Microcysts, foreign-body reaction	Sarcoidosis, etc.
Uchida, 2007 ¹⁵	1	Cheeks and forehead	Cosmetic paraffin injections	Swelling, erythema	Not given	Microcysts, inflammation, positive staining with Oil Red O and Sudan IV	Not given
Anastassov, 2008 ¹⁶	1	Whole face	Injection of “vitamins” to face	Multiple facial irregularities, skin tightness and pain	Multiple irregular asymmetric nodular radiodensities	Microcysts, inflammation	Not given
Kluger, 2009 ³	2	Eyelids, cheeks, chin	Cosmetic surgery	Swelling	Not given	Microcysts, foreign-body reaction, chronic inflammation	Tumors or chronic diseases
Sa, 2011 ¹⁷	9	Periorbital area	Autologous fat injection to the face	Swelling, erythema, mild pain	Ill-defined soft-tissue lesion, heterogeneous high signal intensity (MRI)	Microcysts, foreign-body reaction, fibrosis	Not given
Wang, 2011 ¹⁸	12	Eyelid	Transcanalicular ointment injection after laser canaliculoplasty	Swelling, with erythema and pain	Low-density, well-circumscribed masses	Microcysts, foreign-body reaction, fibrosis, chronic inflammation	Chalazion
Yang, 2012 ¹⁹	9	Periorbital area	Endoscopic sinus surgery	Swelling	Ill-defined, irregular-shaped mass with multiple foci containing fat (CT, MRI)	Microcysts, foreign-body reaction, inflammation, positivity for CD68	Not given
Ryeung, 2013 ²⁰	3	Periorbital area	Autologous fat injection to the forehead	Swelling, redness	Infiltrative mass with indistinct borders (CT)	Foreign-body reaction, chronic inflammation, fibrosis, microcysts, necrosis	Not given

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Table I. Continued

<i>First author</i>	<i>Cases</i>	<i>Locations</i>	<i>Cause</i>	<i>Clinical characteristics</i>	<i>Radiographic characteristics</i>	<i>Histopathological characteristics</i>	<i>Differential diagnosis</i>
Park, 2014 ²¹	2	Cheek	Autologous fat injection to the cheek	Swelling	Irregular-shaped, peripherally enhancing low-density mass (CT)	Microcysts, foreign-body reaction, fibrosis, fat necrosis	Not given
Eun, 2014 ²²	1	Periorbital area	Injection of unknown liquid agent to forehead	Swelling, pain	Not given	Granulomatous inflammation, microcysts, foreign-body reaction	Not given
Ramaswamy, 2015 ²³	3	Periorbital area	Sinonasal surgery with petroleum jelly as nasal packing	Swelling	Minimally enhancing preseptal soft tissue lesion (CT)	Fibrosis, microcysts, foreign-body reaction	Not given
Seo, 2015 ²⁴	27	Periorbital area	Autologous fat injection to face	Swelling, erythema, pain, tenderness	Fat attenuation of round lesions with contrast-enhanced ill-defined infiltrative mass (CT), ill-defined, heterogeneous high, or isosignal intensity with cystic lesions (MRI)	Microcysts, foreign-body reactions, fibrosis	Not given
Jakobiec, 2015 ²⁵	1	Eyelids	Unknown	Swelling, blepharoptosis	Not given	Microcysts rimmed by a lamina of collagen, inflammation	Xanthogranuloma
Kamouna, 2015 ²⁶	3	Lips and surrounding skin	Vitamin E injection to lips	Swelling, induration, erythema	Not given	Not given	Not given
Park, 2016 ²⁷	27	Periorbital area	Autologous fat injection to face	Swelling, blepharoptosis	Focal ill-defined soft tissue enhancing lesion (CT); ill-defined heterogeneous enhanced soft tissue swelling with fat-containing lesion (MRI)	Microcysts, foreign-body reaction, fat necrosis	Not given

CT, computed tomography; *MRI*, magnetic resonance imaging; *PAS*, periodic acid–Schiff.

Table II. Demographic and clinical characteristics of patients with lipogranuloma

	<i>Sex/Age</i>	<i>Sites of lesions</i>	<i>Symptoms</i>	<i>Duration (mo)</i>	<i>Past medical history</i>	<i>Radiographic features</i>	<i>Treatment</i>	<i>Intraoperative findings</i>	<i>Histopathological features</i>	<i>Follow-up</i>	<i>Facial cosmetic procedures history</i>
1	F/43	Both cheeks	Palpable nodules, with fluctuation in size and no pain	4	Noncontributory	Ill-defined swelling in buccal fat pad	Resection of nodule in right cheek	Firm nodule, clearly defined, 1 cm in diameter	Microcysts, foreign-body reaction, chronic inflammation, fibrosis	No recurrence in right cheek, no symptoms in nodule of left cheek	Injection of autologous fat into forehead 6 months prior
2	F/50	Both cheeks	Palpable nodules with slow growth and mild pain	3	Noncontributory	Ill-defined swelling in buccal fat pad, enlarged lymph nodes	Resection of nodules in left cheek	Yellow and firm nodules, 0.5-1 cm in diameter	Microcysts, foreign-body reaction, chronic inflammation, fibrosis	No recurrence in left cheek, no symptoms in nodule of right cheek	Injection of autologous fat into forehead 3 months prior
3	F/47	Right cheek	Palpable nodule with fluctuation in size and no pain	3	Injection of botulinum toxin in canthus twice in a year	Not available	Resection of nodule in right cheek	Firm nodule, 0.5 cm in diameter	Microcysts, foreign-body reaction, chronic inflammation, fibrosis	Nodule was resolved without recurrence	Injection of autologous fat in temporal and of botulinum toxin in canthus several months prior
4	F/35	Right cheek	Palpable nodules with no growth and no pain	6	Injection of botulinum toxin in masseter 3 months prior	Not available	Resection of nodule in right cheek	Cyst-solidary nodule, firmly attached to deputy parotid, 3 cm in diameter	Microcysts, foreign-body reaction, chronic inflammation, fibrosis	Nodule was resolved without recurrence	Injections of autologous fat into forehead and botulinum toxin in masseter 3 months prior
5	F/37	Right cheek	Palpable nodule with no growth and mild pain	6	Sjogren's syndrome	Swelling in buccal fat pad, parotid and submandibular glands	Resection of nodule in right cheek	Solid nodule, close to parotid region, 2 cm in diameter	Microcysts, foreign-body reaction, chronic inflammation, fibrosis	Nodule was resolved without recurrence	Injection of botulinum toxin in canthus and masseter, injection of hyaluronic acid in cheeks 5 years prior; augmentation rhinoplasty 3 years prior
6	F/27	Both cheeks, temporal and paranasal regions	Palpable nodules with slow growth and mild pain	4	Injection of botulinum toxin in masseter twice in a year	Ill-defined swelling in buccal fat pad and pharyngeal space	Resection of nodules in both cheeks	Firm nodules, semitranslucent and jelled, 1 cm in diameter	Microcysts, foreign-body reaction, chronic inflammation, fibrosis	No recurrence in cheeks, partial resolution of nodules in other sites	Injections of botulinum toxin twice in a year, injection of hyaluronic acid 7 months prior

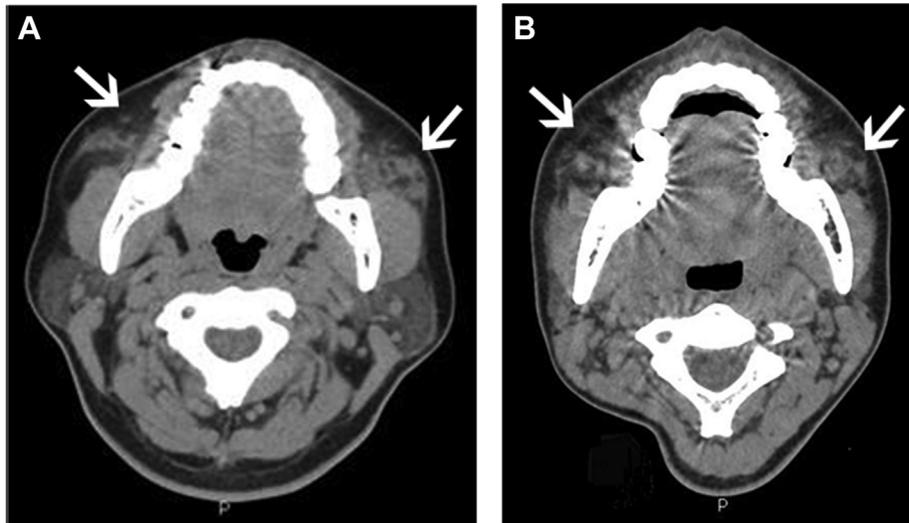


Fig. 1. Computed tomography (CT) scans of (A) patient 2 and (B) patient 6, showing ill-defined masses with heterogeneous density in the buccal fat pad (arrows).

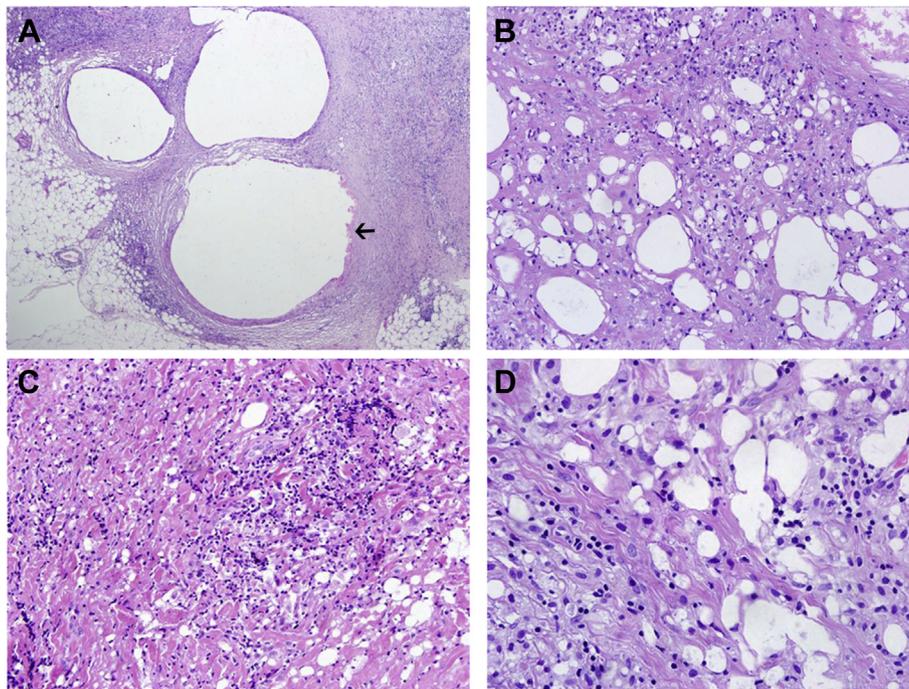


Fig. 2. Pathologic characteristics of the lipogranuloma excised from patient 6. **A**, Variable-sized empty microcysts, one of which was rimmed by a thin layer of eosinophilic crenulated material (arrow) (magnification $\times 40$). **B**, Numerous microcysts surrounded by a mixture of histiocytes, collagen bundles, and inflammatory cells, producing what has been described as a “Swiss cheese” pattern (magnification $\times 100$). **C**, Abundant lymphocytes and foamy macrophages infiltrating the surrounding histiocytes and adipocytes (magnification $\times 200$). **D**, A focal foreign-body reaction dominated by vacuolated macrophages (magnification $\times 400$). (A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide VM03100.)

suckers and a double row of hooklets. The cyst wall has an outer cuticular layer, a middle pseudoepithelial cellular layer, and an inner reticular layer.³⁰ Serologic investigations such as enzyme-linked immunosorbent assay and immunoblot assays

for detection of antibodies to *Taenia solium* in serum can be used to confirm the diagnosis, although not 100% sensitive.³¹

The second factor complicating diagnosis in our cases was the diversity of cosmetic procedures that the patients

had undergone. It is hard for clinicians to identify which cosmetic procedure led to the complication. For example, 4 kinds of facial procedure were performed in our 6 patients: injections of autologous fat, botulinum toxin, and hyaluronic acid, and rhinoplasty.

Facial autologous fat injection for soft tissue augmentation is a technique frequently used for rejuvenation.³² Although autologous fat is considered to be a superb filler because of its biocompatibility, nonimmunogenicity, and biodegradability, complications such as chronic edema, calcification, fibrosis, and acne have been reported after its use.³³ Periorbital lipogranuloma formation after autologous fat injection for cosmetic forehead augmentation is a recently described adverse outcome.^{17,20,22,24,27} Nonviable adipocytes have been mentioned as a possible cause.¹⁷ Successful treatment depends on proper handling and preparation of the fat.³⁴ Injection of microdroplets of damaged and liquefied fat could induce a foreign-body reaction.³⁵ Adipocyte necrosis can be reduced by not freezing the fat tissue before injection.¹⁷ To our knowledge, rare cases of lipogranuloma in the cheek after autologous fat injection have been reported previously.²¹ We speculate that the lipogranulomas in patients 1 to 4 may have been caused by facial autologous fat injection, which is a particularly rare complication.

Injection of botulinum toxin type A (BTX-A) has been widely used for wrinkle correction and treatment of masseter hyperplasia.³⁶ BTX-A has an excellent safety record in cosmetic use. Kim et al.³⁷ reported 184 adverse events (3.73%) among 5310 botulinum toxin treatments; ptosis, hemifacial weakness, and drooling were the most common muscle-related complications. Dissatisfaction and injection-site reactions such as edema and bruising were the most common non-muscle-related adverse events. To our knowledge, there have been no reports of BTX-A being responsible for lipogranuloma.

Hyaluronic acid is a normal constituent of the extracellular matrix. The use of hyaluronic acid is particularly attractive for soft-tissue augmentation, because it provides a natural look and structural mobility.³⁸ To avoid early breakdown by hyaluronidase within the body, hyaluronic acid gels have to be cross-linked, and they typically remain in the tissues for about 6 months after injection.³⁹ At present, approximately 200 hyaluronic acid preparations are available on the market.³⁴ Foreign-body reactions to the different component materials may give rise to granulomas. Hematoxylin and eosin-stained sections show the filler material as lakes or pools of blue colloidal material surrounded by epithelioid histiocytes.⁴⁰ Although patients 5 and 6 received hyaluronic acid injections, the pathology findings were not typical of the granulomas caused by hyaluronic acid.

Augmentation rhinoplasty using alloplastic materials is a relatively common procedure in Asian countries. Silicone is one of the most frequently used materials.⁴¹ Granulomatous reaction to silicone has been reported frequently, and the lesion is termed a siliconoma.^{3,12} Microscopically, siliconoma presents with a “Swiss cheese” appearance characterized by numerous clear vacuoles of varying sizes surrounded by epithelioid histiocytes interspersed with giant cells and inflammatory cells, and is a special type of lipogranuloma.^{3,40} Patient 5 in our series may have developed lipogranuloma as a complication of augmentation rhinoplasty.

Other dermal fillers containing lipid-like constituents, such as paraffin, can also lead to lipogranuloma. In some cases, patients have undergone so many cosmetic procedures that clinicians might be confused about the real cause. In addition, some cosmetologists are not well trained and might use dermal fillers of inferior quality. In some cases, patients might be unaware of the nature or significance of the cosmetic procedures they have previously undergone and therefore omit them or provide an inaccurate history upon questioning by clinicians.

The third factor that may have caused difficulty in diagnosis is that, in the majority of our cases, the lipogranuloma appeared far away from the injection site. In our cases, patients received autologous fat injection in the forehead but developed lipogranuloma in the cheek. Although rare, migration of autologous fat and other dermal fillers is not unprecedented. Lipid materials can migrate to other sites in the body through lymphatic spread.³⁵ Autologous fat injection in the forehead has led to eyelid swelling,³² and axillary lymphadenopathy resulting from lipogranuloma has been reported after silicone breast implant rupture.⁴²

Acknowledging the aforementioned factors, clinicians should consider a diagnosis of lipogranuloma when an inexplicable granuloma is encountered, especially if a prior history of cosmetic procedures is provided.

Lipogranuloma can arise due to an exogenous or endogenous mechanism. Our patients did not have any events related to endogenous lipogranuloma formation, such as trauma. Exogenous materials often provoke an inflammatory reaction.⁴³ Normally, the number of giant-cell macrophages progressively decreases over 6 months and then remains stable. In some cases, however, failure of effective phagocytosis leads to granuloma formation, with aggregates of activated macrophages and surrounding infiltrates of T lymphocytes that secrete cytokines for ongoing macrophage activation. A late-onset T cell-mediated inflammatory granuloma can develop weeks or even years after the initial injection of exogenous material.⁴³

Conservative treatment, such as systemic administration or intralesional injection of steroids, has been recommended as the treatment of choice. Among 21 patients with periorbital lipogranuloma who underwent nonsurgical corticosteroid treatment, 15 patients achieved resolution.²⁴ Surgical excision should be considered for failure or recurrent cases.²¹ If clinicians are familiar with lipogranuloma, they can make the diagnosis by clinical features, medical history, imaging examinations, and fine-needle aspiration findings, in which case they may be able to manage the disease with conservative treatment and avoid unnecessary surgical trauma.

In conclusion, lipogranuloma can develop months to years after a facial cosmetic procedure and can occur at a site distant from the injection site. A thorough understanding of the patient's medical history and the clinical and histopathologic characteristics of lipogranuloma are necessary to make a definite diagnosis and allow appropriate treatment.

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SUPPLEMENTARY DATA

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