Granulomatous foreign body reaction to dermal cosmetic fillers with intraoral migration

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Objective. We report intraoral granulomatous foreign body reactions in patients treated with calcium hydroxylapatite (CHA) or poly-l-lactic acid (PLA).

Study Design. Clinical and histopathologic data were obtained from 25 patients who developed orofacial nodules or swelling after dermal filler injections.

Results. All 25 patients were women aged 35 to 78 years (median, 55 years). All had a history of injection of CHA (n = 13) or PLA (n = 12) to the lips, nasolabial area, or mental area. Two patients developed cutaneous nodules at the sites of injections; all others presented with intraoral nodules (labial/buccal or vestibular mucosa) distant from the site of injections, suggestive of filler migration. Five of 21 cases presented with pain. Histopathologically, CHA presented as a diffuse mass of mauve-gray or beige, nonrefractile spherules, and PLA as rice- or spindle-shaped, geometric, refractile bodies within circumscribed nodules.


In the 1980s, bovine collagen was introduced to treat wrinkles and soft tissue defects, and since that time, many injectable materials have been developed in cosmetic dermatology to smooth wrinkles, treat facial fat atrophy, and provide soft tissue augmentation. In the orofacial region, perioral tissues such as the lips, nasolabial fold, periocular areas, and cheek areas are common sites for dermal filler injection. Cosmetic dermal fillers may be classified into degradable/resorbable fillers (such as collagen and hyaluronic acid) or permanent/nonresorbable fillers (such as silicone). Dermal fillers may also be categorized into filling/volumizing, biostimulatory, or combined fillers based on their space-filling or stimulatory effects on the dermal microenvironment. Hyaluronic acid gel, collagen gel, silicone oil, and polyacrylamide gel are examples of volumizer fillers, and calcium hydroxylapatite (CHA) and poly-l-lactic acid (PLA) have both volumizing and biostimulatory properties.

The present study reports the histopathologic and clinical features of 25 cases of foreign body granulomatous reactions to CHA or PLA, most of which occurred within the oral cavity.

MATERIALS AND METHODS

All cases were accessioned at StrataDx, Lexington, MA, USA, from January 2010 through May 2013. Each patient’s age, gender, lesion site, and lesion size were recorded along with her clinical signs and symptoms. Data regarding the filler injections were obtained from the submitting dentist or from the patient (with permission from the dentist to contact her directly). The histopathologic features were recorded.

RESULTS

Clinical findings

Clinical characteristics of the patients are shown in Table I. All 25 patients were women aged 35 to

Statement of Clinical Relevance

Cutaneous cosmetic filler injections may induce granulomatous foreign body reactions with distinct and readily recognized histopathologic features. Such fillers may migrate from the original injection sites, resulting in nodules that may mimic soft tissue tumors.
78 years (median, 55 years) (see Table I). All patients received their injections extraorally, and 23 presented with intraoral nodules (lip mucosa, maxillary or mandibular vestibular areas, or buccal mucosa). Nodules of the skin developed within the nasolabial fold or chin in 2 patients. In the 20 patients with known dates of injections, the time elapsed from injection to initial detection of the lesion ranged from 2 to 36 months, with an average of 6.5 months. Seven cases were described by their surgeons as yellow/yellowish nodules (Figure 1). Five of 21 patients reported pain.

Thirteen patients received injections of CHA (Radiesse; Bioform Medical, San Mateo, CA, USA) and subsequently presented with a nodule, swelling, or plaque within 2 to 12 months (median, 6 months). As noted in Table I, in 6 patients (cases 1 to 6), the nodules developed in the labial mucosa, skin of the chin, or nasolabial fold, which were in the vicinity of the initial sites of injection. However, in 5 patients (cases 7 to 11), the nodules developed away from the injection sites (the skin of the nasolabial fold, commissure, or mental region).

Twelve patients reported a history of PLA (Sculptra, Dermik, Berwyn, PA, USA) injection with subsequent development of nodules and plaques 5 to 36 months (median, 8 months) after injection. All patients presented with nodules in the maxillary or mandibular vestibular areas or the labial or buccal mucosa, whereas the sites of injection were the skin of the nasolabial fold, lip, or mental region (see Table I). In 2 cases (cases 23 and 24), the filler migrated from the nasolabial fold injection site to the mandibular vestibule.

### Table I. Clinical features of the cases

<table>
<thead>
<tr>
<th>Type of injected filler</th>
<th>Case report No.</th>
<th>Gender/age (y)</th>
<th>Site of lesion/size (cm)</th>
<th>Site of injection</th>
<th>Clinical symptoms and signs</th>
<th>Months between filler injection and first notice</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA</td>
<td>1</td>
<td>F/67</td>
<td>Right upper labial mucosa/1.4</td>
<td>Right upper lip</td>
<td>Painful swelling</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>F/46</td>
<td>Upper labial mucosa/1.2-1.5</td>
<td>Upper lip</td>
<td>Painless swelling</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>F/68</td>
<td>Lower labial mucosa/1.0</td>
<td>Lower lip</td>
<td>Painful swelling</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>F/53</td>
<td>Skin, left chin/2.0</td>
<td>Skin, left chin</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>F/59</td>
<td>Left nasolabial fold/1.6</td>
<td>Left nasolabial fold</td>
<td>Painful firm swelling</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>F/71</td>
<td>Right upper labial mucosa/1.5</td>
<td>Right nasolabial fold</td>
<td>Painless nodules</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>F/48</td>
<td>Mandibular vestibular area/0.5</td>
<td>Labial-mental fold</td>
<td>Painless yellow-white nodule</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>F/71</td>
<td>Upper lip/1.0</td>
<td>Right nasolabial fold</td>
<td>Painless nodule</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>F/54</td>
<td>Right mandibular vestibule, canine area/0.6</td>
<td>Submental fold (last one of multiple injections)</td>
<td>Painless, mobile firm yellow nodule</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>F/51</td>
<td>Left anterior mandibular vestibule/0.6</td>
<td>Skin, near the commissure</td>
<td>Painless, yellow mass</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>F/57</td>
<td>Lower vestibule/0.5</td>
<td>Bilaterally midway between lips and chin</td>
<td>Painless firm mass</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>F/35</td>
<td>Right lower lip/1.0</td>
<td>Unknown</td>
<td>Firm nodule</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>F/55</td>
<td>Right lower lip/0.7</td>
<td>Unknown</td>
<td>Yellowish firm mass</td>
<td>Unknown</td>
</tr>
<tr>
<td>PLA</td>
<td>14</td>
<td>F/69</td>
<td>Right posterior maxillary vestibule/0.6</td>
<td>Right nasolabial fold</td>
<td>Painful firm nodule</td>
<td>24-36</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>F/54</td>
<td>Right buccal mucosa/1.0</td>
<td>Right nasolabial fold</td>
<td>Painful firm nodule</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>F/62</td>
<td>Right labial and buccal mucosa/5.0</td>
<td>Bilateral nasolabial folds</td>
<td>Painless swelling</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>F/51</td>
<td>Right buccal mucosa/1.5</td>
<td>Right nasolabial fold</td>
<td>Painless nodule</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>F/78</td>
<td>Left maxillary vestibule, premolar area/0.7</td>
<td>Left nasolabial fold</td>
<td>Painless, firm, mobile mass</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>F/48</td>
<td>Mandibular vestibule/0.6</td>
<td>Lower lip</td>
<td>Painless firm yellow nodule</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>F/54</td>
<td>Left buccal vestibule/1.3</td>
<td>Left mental area, near border of the mandible</td>
<td>Painless firm nodule</td>
<td>6-8</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>F/56</td>
<td>Left maxillary vestibule/0.8</td>
<td>Lip</td>
<td>Painless, 2 firm yellow movable masses</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>F/60</td>
<td>Left maxillary vestibule, lateral incisor area/1.5 (multiple injections)</td>
<td>Nasolabial fold</td>
<td>Painless firm nodule</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>F/44</td>
<td>Left mandibular vestibule, premolar area/0.3</td>
<td>Nasolabial fold</td>
<td>Painless firm yellow nodule</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>F/40</td>
<td>Right mandibular alveolar mucosa, premolar area/0.5</td>
<td>Nasolabial fold</td>
<td>Painless firm nodule</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>F/66</td>
<td>Left maxillary vestibule, canine area/0.6</td>
<td>Unknown</td>
<td>Firm, multilobulated mass</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

CHA, calcium hydroxylapatite; F, female; PLA, poly-L-lactic acid.
Histopathologic findings

Each of the cases with CHA injection showed a nonencapsulated mass of regularly sized mauve-to-gray or beige spherules, each measuring 20 to 40 μm, surrounded by a histiocytic and giant cell granulomatous foreign body reaction (Figure 2, A). These spherules were not refractile in polarized light and were noted between muscle fibers and within the cytoplasm of giant cells (see Figure 2, B, C). In 11 of 13 cases (85%), there were minimal to moderate chronic inflammation and fibrosis (see Figure 2, D). In all 13 biopsies, CHA was present between skeletal muscle fibers, and myositis was evident in 1 case. Lobules of salivary gland were present in 2 cases, with 1 case exhibiting mild to moderate chronic sialadenitis, although foreign material was not noted within the salivary gland parenchyma.

Each of the cases injected with PLA showed well-circumscribed lobules consisting of ovoid, rice-shaped, or spindle-shaped refractile structures, often within the cytoplasm of giant cells, surrounded by a nonnecrotizing granulomatous reaction (Figure 3, A, B, C). The length and width of these structures varied from 50 to 150 μm and from 15 to 35 μm, respectively. A minimal to moderate chronic inflammatory infiltrate and fibrosis were evident in all cases (see Figure 3, D). Two cases showed necrosis (see Figure 3, E), and 2 cases had scattered eosinophils. Pseudomicrocyst formation (7 cases) and asteroid bodies (5 cases) were evident (see Figure 3, A and F). Skeletal muscle fibers were present in 5 cases that showed PLA particles in between fibers, and myositis was noted in 2 cases. Chronic sialadenitis was seen in 2 of 4 biopsies, which contained lobules of salivary gland tissue, but these did not contain filler material.

A silicone granuloma reviewed for comparison had a diffuse, nonencapsulated mass of macrophages with vacuolated cytoplasm. The intracytoplasmic vacuoles varied in size, and some cells contained numerous small vacuoles, exhibiting a “bubbly” or vesicular appearance (Figure 4, A). The immunohistochemical study for CD163 confirmed the presence of histiocytes (see Figure 4, B), whereas the study for S-100 protein was negative, confirming that the cells were not adipocytic. There was minimal to no nuclear atypia.

DISCUSSION

The use of cosmetic dermal fillers has been on the rise during the past few decades.6 Ideally, injectable cosmetic dermal substances should be biocompatible, safe, and stable at the injection site with no migration potential, and they should induce minimal foreign body reaction.3 Although dermal fillers are generally nonantigenic and nonirritating, acute short-term injection site events, such as discomfort, erythema, bruising, swelling, pain, pruritus, or hematoa formation, may occur.6 More serious complications, such as allergic hypersensitivity reactions, vascular occlusion, necrosis, scarring, or (in rare cases) blindness, have been reported.6-8

Granulomas may occur as intermediate- or late-term adverse reactions occurring weeks or years after treatment.8,9 In this study of CHA and PLA, most patients noted persistent nodules 6 to 8 months (range, 2-36 months) after the injection. With regard to PLA, others have also reported lesions developing at 6 months.2,10 although this is in contrast to the mean of 19 months (range, 6-60 months) reported by Alijotas-Reig et al.11

The clinical incidence of foreign body granulomas associated with cosmetic dermal fillers is infrequent and has been reported to range from 0.02% to 1%, depending on the chemical nature of the dermal filler, its surface structure and properties, and the presence of impurities.7,12 In this study, we reported 25 cases of granulomatous foreign body reaction to CHA or PLA. Interestingly, all but 2 (which presented on the skin of the nasolabial fold and chin) presented as nodules on the mucosal aspect of the lips or intraoral regions. We also described in detail the histopathologic appearance of these fillers.

CHA is composed of microspheres suspended in an aqueous gel carrier (glycerin and sodium carboxymethylcellulose).13 After injection, the aqueous carrier is gradually absorbed over time, but the CHA microspheres serve as a matrix for the production of new collagen.7,11 Lip nodules caused by CHA occur in 7.0% to 12.4% of cases, with early to immediate-stage nodules resolving with massage and later-stage ones being managed with intralesional steroid injections or excision.14,15 Daley et al.14 reported similar foreign body granulomas in 8 cases on the lips or mandibular labial vestibule, and Eversole et al.15 reported an additional 3 cases. In our report, 2 patients presented
with nodules in the upper labial mucosa after injection into the nasolabial folds. Nodules developed in the vestibular areas in another 4 cases, in which there was a history of injection in the skin of the nasolabial, labial-mental, or submental fold areas.

PLA is a synthetic peptide polymer of the \( \alpha \)-hydroxy-acid family that is commonly used in resorbable sutures. It is suspended in mannitol and carboxymethylcellulose. As with CHA, the carrier is rapidly absorbed, and the PLA acts as a stimulant for new collagen production.\(^7,15,19\) Although injectable PLA is considered a biocompatible dermal filler, nodules and foreign body granulomas have also been described.\(^2,10,18,23\) Valantin et al.\(^24\) reported palpable but invisible nodules in 44% of HIV-infected patients who received facial PLA injections, although most of these resolved. In a study by Vleggaar,\(^25\) approximately 3.2% of over 2131 patients reported the presence of invisible subcutaneous papules, and approximately 30% of these resolved; however, 1.2% reported visible subcutaneous papules, and 0.1% of the whole group had histologic confirmation of granulomas. Saylan\(^26\) reported that granulomas developed in 12% of cases, but no histopathologic evidence was shown. In the current study, all PLA cases presented as intraoral nodules, and 11 of those had known sites of injection in the skin.

With only 2 exceptions, the injected CHA and PLA in this study presented as nodules on the mucosal aspect of the lips or intraoral regions, including the vestibular region or buccal mucosa. The “migration” of fillers may be explained by high-volume and high-pressure injection, or it may be caused by muscle movement or gravity.\(^27\) Such mechanisms may result in the occurrence of nodules within the vestibule, deep to the cutaneous sites where the original injection had occurred, or on the labial mucosa when the injection had occurred in the overlying skin. Laeschke\(^27\) suggests the term “dislocation” rather than “migration” for this phenomenon. Migration of dermal filler has been documented previously in the literature.\(^17,22,28\) It is possible that some patients have an innate susceptibility to migration of dermal filler because of differences in the embryologic fusion plane.\(^22\) Cosmetic dermal fillers are widely used, and migration into intraoral locations may raise the suspicion of a mucocele, salivary gland tumor, or soft tissue tumor.

Although all cases showed collections of epithelioid histiocytes with engulfed foreign material, each of the 2 fillers has a distinct morphology.\(^7\) The regularly sized mauve-to-gray or beige spherules of CHA measured 20 to 40 \( \mu \)m, whereas the ovoid, rice-shaped, or spindle-shaped refractile structures of PLA measured 50 to 150 \( \mu \)m in length and 15 to 35 \( \mu \)m in width. The granulomas associated with PLA may contain asteroid bodies, as noted here and in previous reports.\(^2,20\) The histopathologic features of these 2 dermal fillers are
distinct from those of silicone granulomas, which are characterized by lipid-like vacuoles within the histiocytes. Furthermore, the granulomas formed by CHA were poorly circumscribed, whereas those of PLA were generally well circumscribed.

Variable degrees of chronic inflammation and fibrosis were noted in a majority of cases. The reason for such an inflammatory response to biocompatible materials is still unclear, but the volume of injected dermal fillers, repeated injections using the micro-droplet technique (repeated injections over a larger surface may stimulate more macrophage activity than single injections), impurities within a filler, incorrect depth of injection, or the large size of some particles may play a role.\textsuperscript{10,12}

In conclusion, CHA and PLA produce granulomatous inflammation with distinct and readily recognized features. Such fillers may migrate from the original injection site, resulting in painful or painless nodules that may mimic soft tissue tumors.

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REFERENCES


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