

The Histological Aspects of Fillers Complications

Ute S. Zimmermann, MD, and Thierry J. Clerici, MD

The histological aspects of resorbable heterologous fillers (bovine collagen, acid hyaluronic), autologous fillers (lipofilling, dermis-fat graft), biodegradable fillers (New-Fill), and permanent fillers (silicone, Artecoll, Evolution, Aquamid, DermaLive, DermaDeep, Bioplastique, Paraffin) are described. This article relates the morphological aspect of these materials, the normal tissue reaction after injection, and its chronological evolution as the morphological aspects from the different side effects, more frequently observed for the permanent fillers. They mainly consist of granulomatous reactions which may appear long after injection.

Semin Cutan Med Surg 23:241-250 © 2004 Elsevier Inc. All rights reserved.

KEYWORDS side effects, filler, bovine collagen, hyaluronic acid, biodegradable fillers, permanent fillers

For more than a century, an ideal filler has been requested for cosmetic and also for reparation purposes. Historically, different products were used, such as ivory, paraffin, and silicone. Actually there are two main categories of injectable fillers: biodegradable products persisting for a few months to a few years, and nonresorbable or permanent products which cannot be eliminated.

Most fillers seem to be well tolerated and, regarding the number of injections, few complications with histological analyses are reported in the literature. However some cases are probably not reported because available information about injections and agents are difficult to obtain. The pathological report may be an important document to identify the nature of the injected filler and to evaluate the long-term side effects of the product. It may sometimes be used for legal actions.

The usual nonspecific and transitory side effects after injections of all kinds of filler are not discussed here. They consist of erythema and swelling, and their duration and intensity depend on the individual and the product, varying from a few days for collagen to a few weeks for nonresorbable fillers. Usually, no biopsy is performed. The few histological examinations available are conducted on animals and human volunteers, showing the injected material and a slight lymphohistocytic periappendageal and perivascular infiltration.^{1,2,3}

Resorbable Fillers

Lipofilling

Autologous fat is obtained from the lower abdomen and, in the reported case, injected in the lip. Histological analysis shows a normal, glandular lip tissue clearly distinguishable from the transplanted fat. The latter has a normal appearance, with most adipocytes ranging in size from 40 to 80 μm . Connective tissue and collagen are almost absent, and only small blood vessels are seen between the fat lobules.⁴ No histological analysis of complications has been published.

Dermis-Fat Graft

Dermis-fat graft is obtained, when possible, from a previous scar and implanted in the requested sites. Histological examination, available in two cases, reveals nothing or a slight lymphocytic inflammation.⁴ No microscopic examination from complications is found in literature.

Collagen (Bovine Collagen Implant)

Injectable collagen is a reconstituted, purified, enzyme-digested, bovine dermal collagen suspended in phosphate-buffered saline with 0.3% lidocaine. Zyderm I, approved by the FDA in 1981, contains a collagen concentration of 35 mg/mL. Rapid resorption led to the development of Zyderm II and Zyplast, which were FDA-approved in 1983 and 1985, respectively. Zyderm II is similar to Zyderm I, but contains a higher concentration of collagen (65 mg/mL). Zyplast differs from Zyderm I and II in that it contains glutaraldehyde cross-linked collagen, and the treatment with glutaraldehyde increases stability and longevity of the implant,

SCP d'Histopathologie, Paris, France.

Address reprint requests to Ute S. Zimmermann, MD, SCP d'Histopathologie, 56, rue de la Roquette, 75 011 Paris, France. E-mail: ute.zimmermann@noos.fr

which is less susceptible to collagenase. Zyplast has a collagen concentration of 35 mg/mL.

Zyderm and Zyplast are injected intradermally. Zyderm is infiltrated into the papillary dermis, whereas Zyplast is placed into the midreticular dermis and the subcutaneous interface.⁵

The Normal Aspect after Collagen Injection

In a hematoxylin-eosin section, the collagen implant appears as an irregular, variably sized island of homogenous eosinophilic material that stains lighter than the normal collagen, and the bundles are thicker and more amorphous than the native collagen. The implant is acellular and avascular and tends to show cleavages.^{3,6} Zyplast is usually found in larger deposits with a more distinctive fibrillar structure than Zyderm. There is no evidence of active degradation or foreign body reaction to the injected collagen. With polarized light, it is only weakly birefringent in contrast to the normal surrounding collagen.^{3,7,8} Special histological stains as colloidal iron counterstained with acid fuchsin and Masson's trichrome stain may more clearly distinguish the injected collagen from native collagen.³

After injection of Zyderm, a mild perivascular and periappendageal lymphohistiocytic infiltrate, which gradually resolves in 3 months, is described. This inflammatory reaction is found in asymptomatic patients and are unrelated to the implanted material.^{7,9} Most authors observed collagen deposition in the dermis, although Stegman et al. identified it also in the subcutaneous tissue, interpreting it as a migration of the injected collagen.⁷ Zyplast persists up to 12 months, whereas Zyderm is surrounded by fibroblasts and resorbed in 3 months. After Zyderm injection, Burke et al.¹⁰ detected host granulation tissue and the synthesis of fine fibrillar collagen in the injection site, whereas others could not demonstrate similar findings.¹

Complications

Several types of side effects are related in the literature: their histological aspects may be a nonspecific inflammatory infiltrate in the dermis, a granulomatous reaction, and less frequently, abscess formation or exceptionally, local necrosis. For the latter, only one histological report is published.

Nonspecific Inflammation

Intermittent localized swelling at the injection site, which may recur for up to 3 years and lasts from hours to weeks and is often accompanied by erythema and induration, shows a nonspecific aspect on histological examination. It consists of a superficial and mid-dermis perivascular and periappendageal mononuclear infiltrate. The collagen implant is infiltrated by neutrophils, lymphocytes, histiocytes, and some eosinophils.¹¹

Granulomas

The granulomatous side effect occurs generally during the first months following injection consisting of erythematous,

indurate and swollen injection sites, or nodules. They may exceptionally be observed years later.

In the early cases, the histological analysis reveals a granuloma made by an inflammatory reaction that surrounds and only minimally invades the implant. The infiltrate ranges from monocytes only to a mixture of round cells, a varying, sometimes important, number of eosinophils, neutrophils, foreign-body giant cells, and sometimes plasma cells. The cellular infiltrate described by Ackerman also consists of epithelioid histiocytes. At the periphery of the zone of granulomatous inflammation, there sometimes are signs of fibroplasia. The surrounding dermis contains a dense perivascular, mixed-cell infiltrate.¹² No mucin deposits are detected. The injected collagen is usually brightly eosinophilic. It lacks the characteristic fibrillar nature of native collagen. Deposits of bovine collagen rapidly become less distinct.

Morgan differentiates a palisaded granuloma, occurring mainly after 2 to 3 months after injection and located in the mid to deep dermis, and a diffusely organized granuloma, more prevalent within 2 weeks after implantation and seen in the deep dermis and the subcutis.³

Very rare cases of late granulomas, appearing 2 to 10 years after injection, are reported; they may extend into the superficial and deep muscle. Microscopic examination reveals a dense granulomatous inflammatory infiltrate, visible in the dermis and the subcutaneous fat, consisting of noncaseating granulomas composed of histiocytes, epithelioid cells, and multinucleated histiocytes. Focal collection of lymphocytes were present between some of the granulomas. No pathologic organisms are seen. There is no birefringent material with polarized light examination.¹³ Constantinides et al. report empty vacuoles with foreign-body granulomas in the deep subdermis. Arguments for a siliconoma have not been detected.¹⁴

Granuloma Annulare

Rapaport et al.¹⁵ reported the case of a dense palisading granuloma within the dermis, diagnosed as granuloma annulare. The lesion appeared at the site of the collagen test injection in a patient with history of granuloma annulare. The physiopathological mechanism might be similar to the one described for granuloma annulare appearing after cutaneous inflammation such as herpes infection¹⁶ or traumatic events.¹⁷

Abscess Formation

Abscess formation is a rare complication occurring between 7 days and 22 months after treatment and may persist for weeks and periodically recur for months. The histological aspect shows numerous neutrophils, round cells, plasma cells, giant cells surrounding particles of injected collagen, cellular debris, fibrin, and hemorrhage. The inflammatory reaction is restricted to the implant or involves the adjacent tissue. The surrounding dermis is richly vascularized, and plasma cells and superficial histiocytic granulomas may be identified. When the subcutis is involved, some fat cell necrosis and vascular dilation may be observed. When the in-

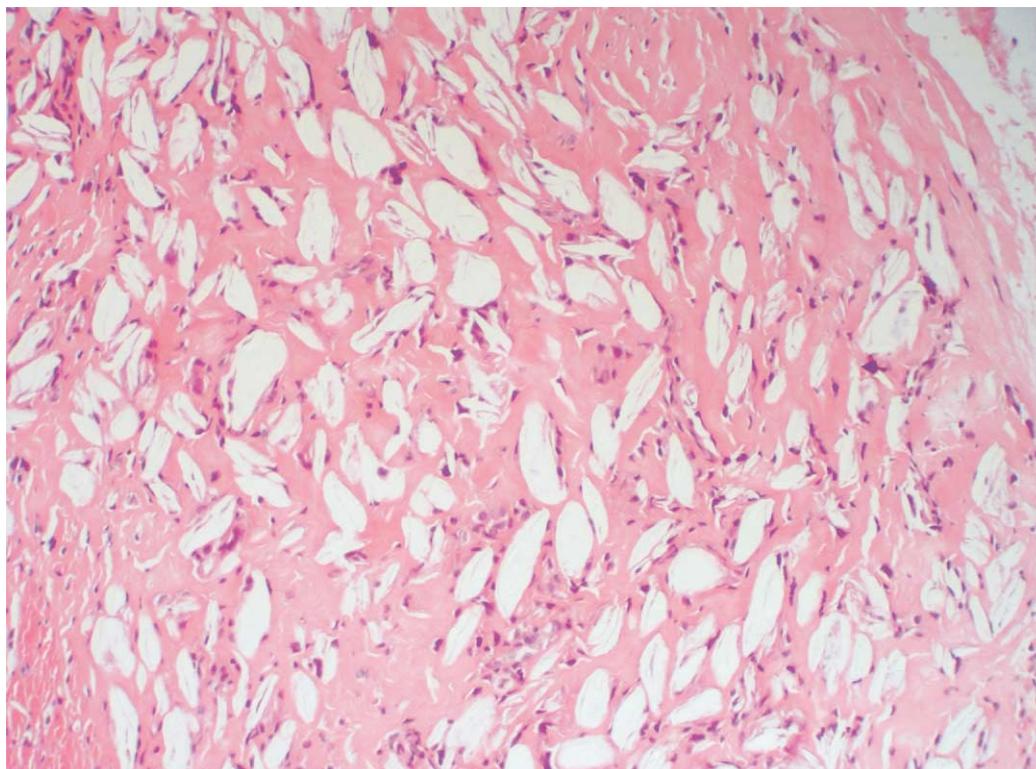


Figure 1 (medium x) New-fill. (Color version of figure is available online.)

filtrate extends into the overlying epidermis, a resulting eruptive event may be seen. The purulent material, when cultured, has not revealed any consistent findings.¹⁸

Local Necrosis

Local necrosis, especially the glabellar area, increased since the introduction of Zyplast in 1985. The risk of the arterial occlusion due to the deeper injection in this area of poor vascularization is proven. Only very few histological descriptions are available showing the implant materials in the lumen of the small arteriolar vessel, leaving only the medial wall elements identifiable. No inflammatory or necrotic process was apparent immediately surrounding the emboli. Recavitation or regrowth of the luminal endothelium may be seen.¹⁸

Autologous Collagen (Autologen)

Autologen is an injectable autologous human tissue matrix, primarily composed of intact collagen fibrils. It is processed from the patient's own skin.¹⁹ The morphological aspects of the inflammatory and fibroblastic reactions are similar to those described for the bovine collagen.²⁰

Hyaluronic Acid

Two different types of hyaluronic acids (HAs) were launched on the market: HA derived from animal and non-animal-derived HA. Restylane (Q Med, Sweden) is a partially cross-linked HA processed from bacterial (*Streptococcus*) fermentation, containing a concentration of 20 mg/ml of HA. Juvederm (LEA-Derm, France) is also a non-animal-derived

HA with a concentration of 24 mg/mL. Hylaform (Biomatrix, USA) derives from rooster's comb and it is cross-linked; it contains a concentration of 5.5 mg/ml of HA. Longevity of HA will depend of the stabilization process. HA is injected most often into the dermis, but sometimes more deeply.

The Normal Aspect after Hyaluronic Acid Injection

Histological aspects from human volunteers show the HA in the dermis with little foreign body reaction made of macrophages and a few multinucleated giant cells. There is no fibrosis.^{9,21} While some authors still mention the persistence of the product in a more watery appearance 1 year after injection,²¹ others do not identify it after a period of 9 months.⁹

The histological aspect and the chronological modifications are described after injection in animals.²²

Complications

The reported side effects are redness, intermitting swelling, pruritus, and nodules sometimes leading to abscess formation. They develop several days up to 1 year after injection.

The histological examination always shows inflammation, varying from a light chronic inflammatory infiltration without foreign-body reaction²³ to a moderate or dense inflammatory reaction made of lymphocytes, plasma cells, and a variable amount of macrophages. The foreign-body reaction, when present, may be sharply demarcated, like a nodule surrounding the injected material. The latter stains intensely with Alcian blue at pH 2.7, which confirmed it as HA.²⁴

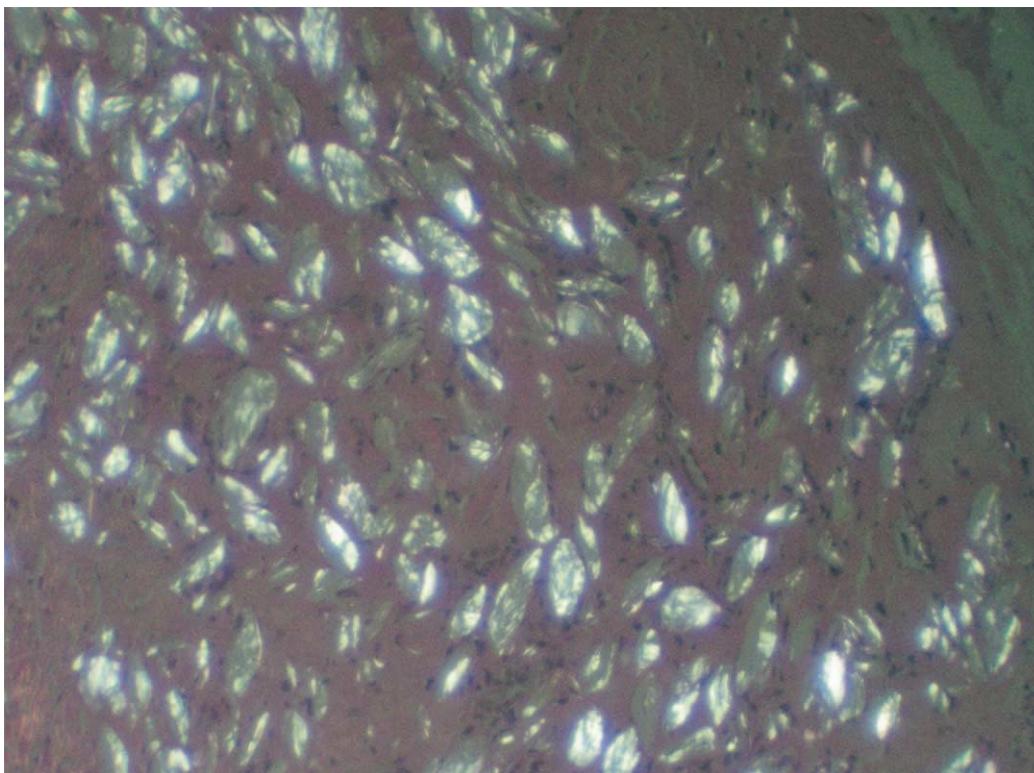


Figure 2 (medium x) New-Fill, polarized aspect. (Color version of figure is available online.)

Eventually siderophages but no eosinophils are identified.²⁵ The inflammatory reaction may extend into the subcutaneous fat. Fibrosis may be prominent and involve the lower dermis.

Only two cases of abscess-like lesions are reported, without characteristic histological features. In one case, the cultured drained material was negative²⁶ and no biopsy was performed; in the other case, microscopic examination was made after the abscess resolved following drainage. The sample showed a foreign body granuloma and did not mention any neutrophils.²⁷

Similar to collagen injections, exceptional cases of cutaneous necrosis are published. Cases consist of an arterial embolization²⁸ or compression,²⁹ caused by HA injection, and a case of venous occlusion with varix, without residual detectable HA after appropriate stains.³⁰

One case of scleromyxedema in the face appearing 9 months after injection of HA was reported. The authors suggested that the nature of the injected product may have caused a delayed granulomatous reaction possibly leading to scleromyxoedema.³¹

New-Fill (Poly-L-Lactic Acid)

New-Fill is a biodegradable filler composed of polylactic acid (PLA) microspheres (2-50 μm) suspended in a mannitol and carbomethoxycellulose solution, which was created and admitted in 1999 in Europe. After injection, the carrier solution is rapidly resorbed, and then the slow process of biodegradation of microspheres takes place. It consists of phagocytosis by macrophages, transforming them in particles of small size

and irregular shape. These structures are birefringent when analyzed in polarized light. A PLA-induced synthesis of collagen is associated with the biodegradation, aimed to produce the cosmetic result.³²

Normal Aspects of New-Fill

Histological examination on a human volunteer shows a fine capsule around the implant. After 3 months, the microspheres remain spherical and are surrounded by macrophages, giant cells, and some lymphocytes. After 6 months, most microspheres show a porous surface structure, are fissured and sometimes deformed, and are surrounded by macrophages and small giant cells. The PLA is likely dissolved by hydrolysis and extracellular enzymes and subsequently broken down by macrophages. After 9 months, the degradation of PLA microspheres is complete. No remnant of scar fibrosis is found.⁹

Complication

When adverse reaction occurs, the histological sample shows numerous giant cells including multiple translucent particles of different sizes, some of them fusiform or spiky, birefringent in polarized light examination. Some giant cells contain asteroid bodies, and the well-limited granulomatous patches are sprinkled by a mild lymphocytic infiltrate.³² These aspects may be present at least 18 months after injection (personal data, unpublished) (Figs. 1 and 2).

Permanent Fillers

The previous products and most of the following products may be identified by their characteristic morphological aspects. An inflammatory and fibrotic reaction is developed at their contact, depending on the nature of the product and the patient. Lombardi et al.³² proposed a classification of these granulomas based on the morphological aspects of the fillers and the inflammatory reaction.

Artecoll (Polymethyl Methacrylate)

Artecoll is made of polymethyl methacrylate microspheres of 30 to 40 μm with a smooth surface (25%) suspended in bovine collagen (75%) used as a carrier gel. It must be injected subdermally, at the junction of the dermis and the subcutaneous fat. The collagen is removed within months and is replaced by granulomatous reaction embedded within collagen bundles. The subsequent complications were reduced since 1994 because of an improvement in the surface of the PMMA microspheres.

Normal Aspects of Artecoll

Examination of biopsy specimens in human volunteers shows monocytes invading the implant after 3 days; then they differentiated to fibroblasts the following 6 days. All interspaces are filled by fibroblasts after 9 days. After 2 months, a fine fibrous capsule surrounds each microsphere, and monocytes and histiocytes decreased. All injected collagen is phagocyted by macrophages after 3 months. This fibrozing phase seems to end after 4 months, and the histological aspect is unchanged later. A small number of foreign body cells decreases to a stable amount.^{2,9} Studies in animals are reported from Lemperle et al.³³ and McClelland et al.³⁴

Complications

The clinical complications, where histological analysis was performed, consist of induration and nodules appearing 3 to 24 months after injection. Pollack claims that most of the complications relate to a too-superficial injection.³⁵

The histological analysis always identifies the injected product; the varying degree of inflammatory reaction and fibrosis led Lemperle et al. to propose the inflammatory granuloma and the hypertrophic scarring.^{36,37}

Inflammatory Foreign Body Granuloma

The striking morphological aspect is a diffuse and nodular inflammatory reaction developed in the dermis, in the subcutaneous fat, and sometimes in the skeletal muscle³⁸ and the adjacent sweat glands,³⁹ intermingled with many round, apparently empty round, vacuoles of nearly the same size. At scanning magnification, they may be confused with normal adipocytes. Closer inspection shows epithelioid cells and a few multinucleate giant cells with occasional asteroid bodies in their cytoplasm, intermingled with a lymphocytic infiltrate, sometimes sparse and/or realizing nodules and follicles,³⁹ all of which surrounded the round vacuoles. All au-

thors but Lemperle et al.^{36,37} described occasional eosinophils in the inflammatory reaction. After lowering the condenser, round, sharply circumscribed, translucent, non-birefringent foreign bodies were detected inside the cystic spaces. The vacuoles are singly or in small clusters embedded in a loose sclerotic stroma.^{37,38,40-42} Some authors relate a pale basophilic material inside the multinucleate giant cells⁴³ or outlying the granuloma.³⁹ Others found amorphous feathery eosinophilic material inside in round, apparently empty, structures of almost identical size⁴⁴ (Fig. 3).

The Hypertrophic Scarring

The histological aspect corresponds to an intense fibroblastic activity, with thick bands of collagen fibers and rare foreign body granulomas between the clusters of the injected product.^{36,37}

Ultrastructural Examination

The ultrastructural examination, performed in some cases, reveals microspheres in the cytoplasm of giant cells and macrophages, that supposes degradation.^{34,42,43} This hypothesis is refuted by others.^{36,37}

DermaLive, DermaDeep (Polyethyl Methacrylate)

DermaLive and DermaDeep are made of pure HA produced by cell-culture bacterial fermentation (40 and 60% of the volume, respectively) and an acrylic hydrogel (copolymer of hydroxymethacrylate, HEMA, and ethylmethacrylate, EEMA), 45 to 65 μm and 80 to 110 μm . Acrylic hydrogel particles are irregular with smooth walls. DermaLive must be injected into the deeper layers of the dermis, at the junction between the dermis and the hypodermis. DermaDeep must be injected into the subperiosteal layer or the hypodermis. Long-range side effects appear on average 6 months after injection, consisting of indurations, nodules, swelling, and sometimes redness.⁴⁵

Normal Aspects of DermaLive and DermaDeep

The histological aspect of the product shows polygonal, translucent, and irregular particles, 20 to 120 μm in size, which appear like broken glass or gravel, packed in clusters, with minimal growth of fibrous tissue, cells, and blood vessels. Few macrophages are found, a fine network of elastic fibers and no apparent capillaries and no strong fibrous capsule. The HA is separated and surrounded by macrophages, which disappeared after 3 months. After 9 months, only a few small clusters of DermaLive with rounded corners and ridges, many macrophages, and lymphoid cell clusters could be detected. The few giant cells contain abundant asteroid bodies in their cytoplasm. Some pointed particles had a tendency to irritate the surrounding soft tissue, which shows clear evidence of low-grade inflammation.⁹

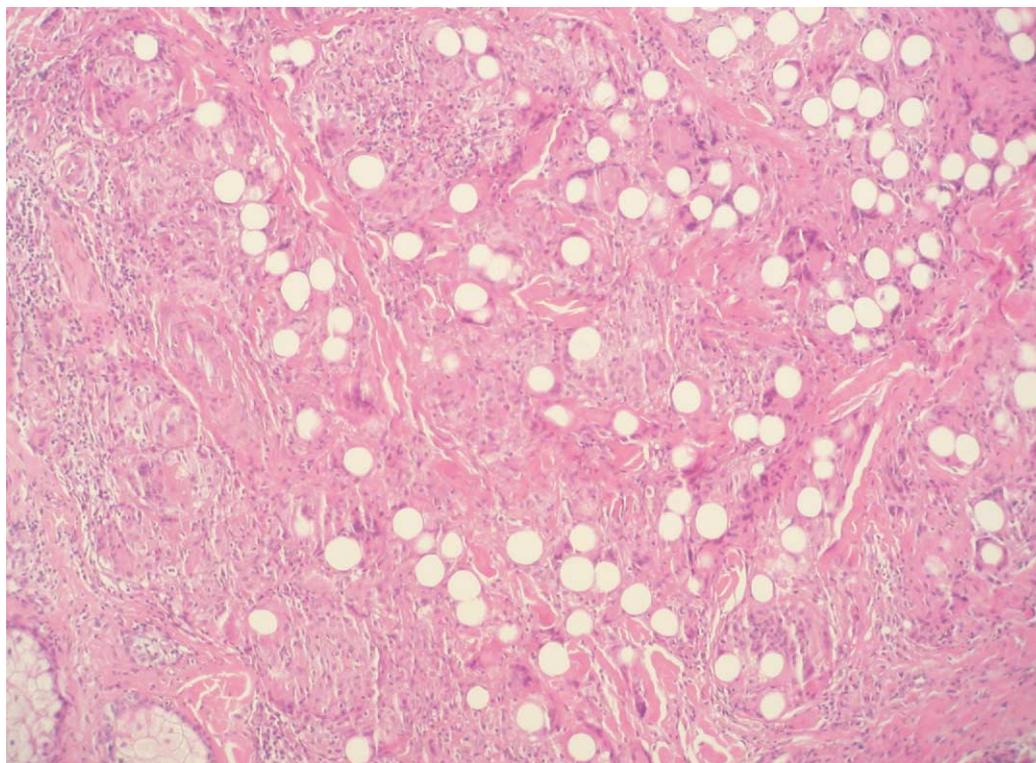


Figure 3 (low x) Artecoll. (Color version of figure is available online.)

Complications

When induration or nodules occur, the histological examination shows a nodular granulomatous infiltrate composed of epithelioid histiocytes, multinucleate giant cells with asteroid bodies in their cytoplasm, and some lymphocytes. Between the inflammatory cells, multiple extracellular foreign body particles were seen. They are small, of slightly different sizes, polygonal or irregular shaped, pink, translucent, and nonbirefringent, found within small cystic spaces resulting from retraction secondary to fixation.^{32,41} Transepidermal elimination of the product may occur (personal data, unpublished) (Fig. 4).

Silicone

Silicone (polydimethyl siloxilane) is a polymer from a family of the chemically related organosilicon compounds that may exist in any state from a fluid to a solid. Medical-grade silicone refers to a pure and sterile preparation with constant viscosity of 360 centigrades.

The reaction to silicone gel and liquid is different from that produced in response to silicone elastomer because the exuberant foreign body giant cell reaction seen with the latter is typically absent in the former.^{1,46,47}

Normal Aspects of Medical-Grade Silicone

The injected material forms optically empty vacuoles of various sizes, encapsulated by fibroblasts and collagen fibers. Macrophages and giant cells are seen. Their cytoplasm is foamy or vacuolated, and asteroid bodies are detected. Later

fibrosis becomes prominent surrounding the clusters of vacuoles.⁹

Complications

The liquid form (dimethyl polysiloxane) has been used extensively in some countries during the past decades for soft-tissue augmentation. Although considered biologically inert, this material has been reported as potentially inducing a granulomatous inflammatory response of variable severity after tissue injection.⁴⁷ The reactions may develop many years after injection. Treatment-site reactions including pain, erythema, ecchymosis, pigmentation, induration, and migration of the injected material to distant locations, causing facial deformity, are common. More severe complications such as granulomatous reaction, presenting clinically as recurrent cellulites with nodule formation, ulceration, and local lymph node enlargement, have also been reported, as well as tissue scarring, embolism, acute pneumonitis, and granulomatous hepatitis.^{48,49}

The main histological aspect identified in biopsy specimens is cystic spaces, which often appear empty because silicone is lost in processing, dissolved by xylene. The vacuoles, involving the dermis, the subcutaneous tissue, and the skeletal muscle, are round to oval. They may be relatively small and uniform, or, depending on the amount of material introduced into the tissue, may become larger with more variation in size and shape. They are described as “Swiss-cheese”-like, sometimes related as a residual glassy-appearing material found inside (silicone elastomer). Some histio-

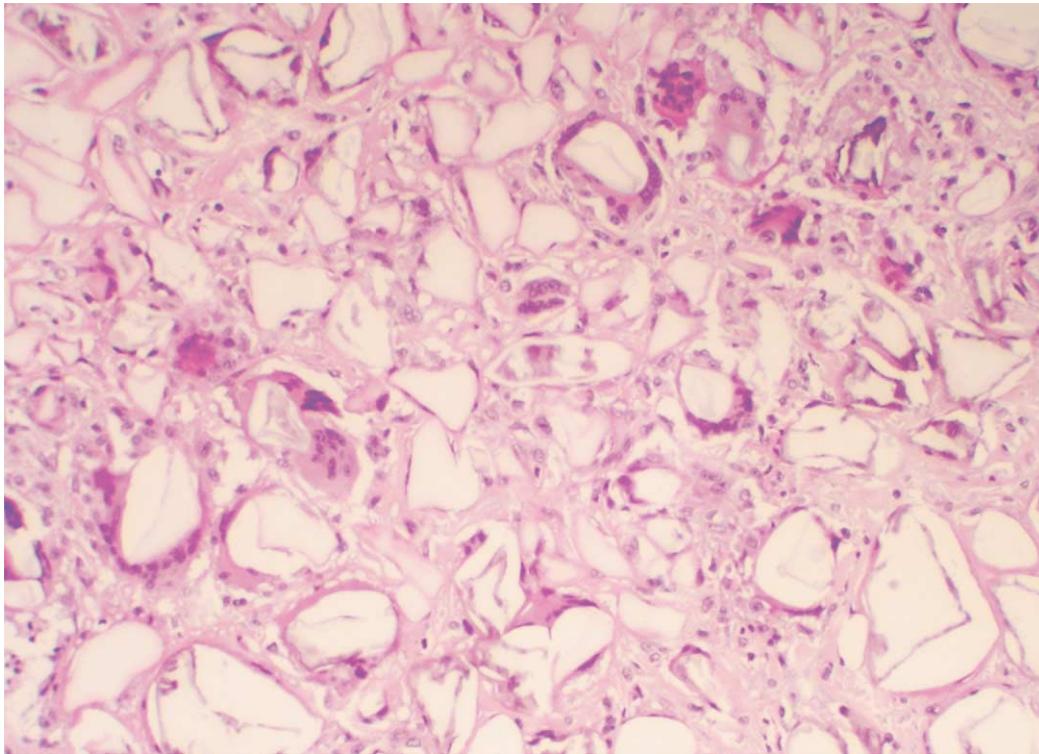


Figure 4 (medium x) DermaLive. (Color version of figure is available online.)

cytes surround the cystic spaces. The amount of the inflammatory reaction is varying. Macrophages often show a foamy aspect or have a multivacuolated cytoplasm. Multinucleated giant cells may be lacking or be numerous and can take a daisy-like aspect: numerous clear peripheral vacuoles surrounding a central cytoplasmic residue filled with closely cropped nuclei.⁹ Asteroid bodies in the cytoplasm of the epithelioid histiocytes and the giant cells are usually present. The inflammatory reaction may include eosinophils. The stroma is sclerotic, surrounding the cavities^{1,3,41,46-48,50,51} (Fig. 5). Silicone can be detected by scanning electron microscopic and energy dispersive x-ray analysis (EDXA).^{46,52}

In some cases, angulated, translucent birefringent bodies are also detected in the cytoplasm of multinucleated cells. They are impurities in silicone,⁴¹ suggesting low-grade silicone or modified silicone with contaminants.⁴⁶ Ackerman found that these impurities are not refractile when examined with polarized light.⁵³ Ficarra et al. described small fragments inside vacuoles of varying sizes which are translucent refractile nonbirefringent foreign material when viewed with polarized light.⁴⁷

Some infrequent adverse effects are reported as ulceration appearing several years after silicone injection. The histological aspect is not very different, mentioning additional plasma cells.⁵⁴ An abscess-like formation is also mentioned. The routine histology reveals spherical homogenous foreign body inclusions of 0.02 to 0.05 mm in diameter in fibrous connective tissue. The inclusions are surrounded by moderate infiltration of lymphocytes in several areas indicating an inflammatory reaction. In addition, numerous multinuclear giant cells are observed.⁵⁵

Pimentel et al. reported a case where silica granulomas and a nodule in the face appeared simultaneously at the injection site from silicone made 7 years before. The histological aspect is similar to the previously described ones.⁵⁶

The morphological aspect of the solid areas made of relatively small, uniform cystic spaces infiltrate soft tissues, as seen for the silicone, may imitate low-grade liposarcoma.⁵⁷ In siliconoma, the vacuolated cells express CD 68 and lysozyme. There was no expression of the PS 100. Electron probe analysis confirms silicone.⁵⁸

The other differential diagnoses are noncaseating granulomas as seen in the Melkerson–Rosenthal syndrome, sarcoidosis, and low-grade fibrosarcoma.⁴⁷ Foreign-body granulomas paraffinoma, talc granuloma, and granulomatous response to silica, silicone, and bovine collagen can be differentiated from silicone granuloma through their histological aspects and the use of polarized light.

Bioplastique

Bioplastique consists of 38% biphasic polymer, textured polydimethylsiloxane (silicone) particles of controlled size from 100 to 600 μm , suspended in a 62% bioexcretable gel carrier. Bioplastique is injected into the subcutaneous tissue.

Normal Histological Aspects

On histological samples, the Bioplastique particles are jagged, translucent, nonbirefringent inclusions inside cystic-like structures of varying sizes.

The early inflammatory reaction is polymorphic, dissipating after a few days and followed by chronic inflammatory

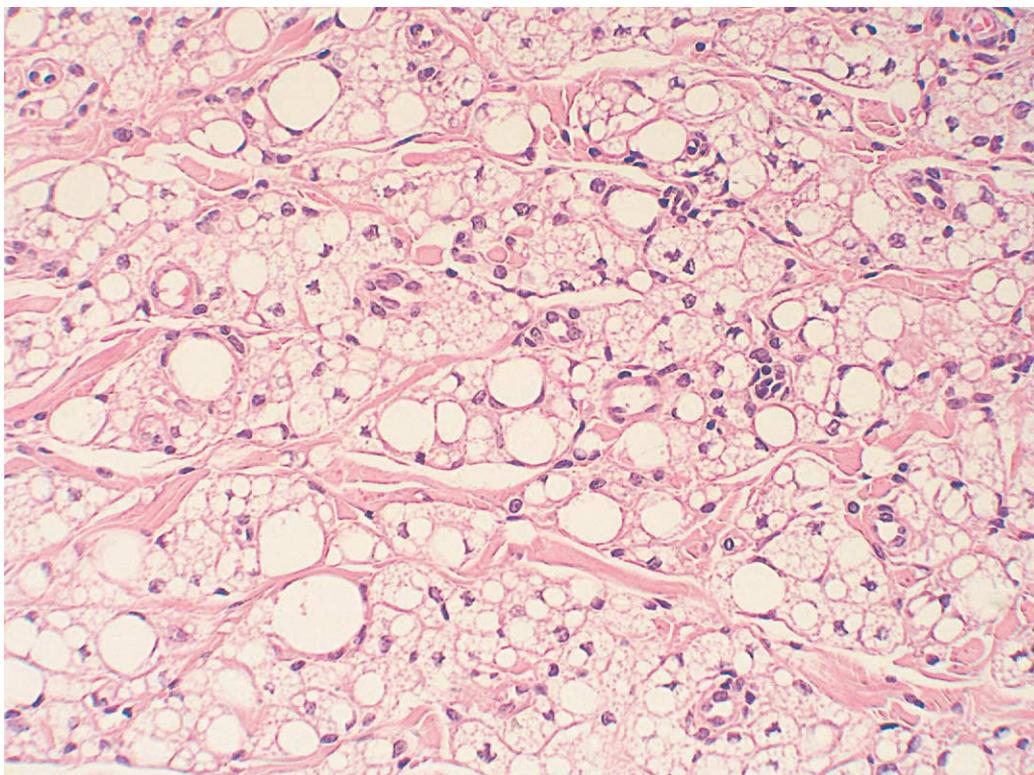


Figure 5 (medium x) Silicone. (Color version of figure is available online.)

changes consisting of monocytes, foreign body giant cells, and fibroblasts. Epithelioid differentiation of the histiocytes and immature collagen is noted after 4 weeks. No asteroid bodies are visible in the cytoplasm of the foreign body giant cell. The chronic inflammatory is slight. Collagen deposition increases,^{4,59} forming a fibrotic capsule around each textured particle as a result of the naturally occurring foreign body reaction.^{40,60,61} Normal histological aspects are also described after Bioplastique injection in animals.⁶²⁻⁶⁴

Bioplastique Granuloma

The microscopic examination of excised indurate nodules reveals a nodular granulomatous infiltrate embedded in a rather dense sclerotic stroma situated in the reticular dermis, in the subcutaneous tissue, and sometimes in the upper skeletal muscle. Numerous, cystic-like structures of varying sizes are identified, completely surrounded with multinucleate foreign-body giant cells. They are dispersed solely or disposed in small clusters. Inside the cystic-like structures, jagged translucent nonbirefringent inclusions are detected. Asteroid bodies are identified in the cytoplasm of the giant cells, accompanied by a moderate dense lymphocytic inflammatory infiltrate mixed with eosinophils.^{38,60} The latter are not mentioned in the case reported from Hoffmann et al.⁴⁰

Paraffin

The main morphological aspects of paraffinomas or sclerosing lipogranulomas are briefly described because of historical injections of paraffin or a foreign substance containing long-chain acyclic hydrocarbons. Mineral oils cannot be broken

down and produce a foreign-body inflammatory reaction with phagocytosis.

The clinical course may be relatively quiet, and the histological analysis, many years later for other purposes, shows a “burned-out paraffinoma,” consisting of vacuoles of varying size and shape surrounded by a sclerotic stroma made of hyalinized collagen. When inflammation occurs, after various periods of time, the microscopic examination reveals a dermal and subcutaneous inflammatory reaction of varying degrees. It consists of lymphocytes, histiocytes, plasma cells,⁶⁵ and multinucleated foreign-body giant cells surrounding oil droplets which are removed during processing, leaving clear spaces. Typically, there are numerous foamy macrophages (lipophages) and epithelioid cells. A hyalin fibrosis is dissociated by clefts and cystic spaces.^{66,67}

Aquamid Polyacrylamide Gel

Aquamid polyacrylamide gel (PAAG) is a jelly-like transparent substance consisting of 95% water and 5% hydrophilic, biocompatible, cross-linked polyacrylamide polymer, which contains no particles.⁴ It is nonresorbable. It must be injected strictly subcutaneously.⁶⁸

Normal Aspects of Aquamid Polyacrylamide Gel

Histological examination on human volunteers shows that acrylamide gel is difficult to detect after 1 month. The injected, nonstainable transparent gel produces only a fine fibrocellular capsule. After 3 months, no further histological

reaction occurs outside the implanted site, in particular, no foreign body reaction. After 6 and 9 months, Aquamid is dispersed into the skin and is surrounded by macrophages and fibroblasts. The histological aspect resembles that of injected fluid silicone.⁹

Complications

Severe granulomatous reactions were reported, appearing a few weeks after injection. During incisional biopsy, a small abscess-like lesion was drained. The histological examination reveals granulomas consisting of histiocytes, foreign body giant cells, fibroblasts, and lymphocytes surrounding amorphous material. There is no fibrosis. No acid-fast rods are detected.⁶⁹

Evolution

Evolution is a suspension of 6% polyvinylhydroxyde (PVOH) microspheres (5 to 80 μm) in 2.5% polyacrylamide gel.

Histological examination in a human volunteer shows the beads, most of them 30 to 40 μm in diameter, within the clear acrylamide gel surrounded by an almost invisible fibrous capsule. Each droplet, 3 to 5 mm in size, was encapsulated with a very fine layer of fibroblast and fibers without ingrowth in the implant. No foreign body reaction is detectable. A few single microspheres outside the implant site are covered with a fibrin layer or has attached macrophages and fibroblasts. After 6 months, macrophages and multinucleated cells have phagocytosed most of the carrier gel. It is replaced at the outer layers by a granulation tissue. After 9 months, the implant is totally infiltrated by macrophages, fibroblasts, and giant cells. The surface of the microspheres is still intact after 9 months.⁹ To our knowledge, no histological analysis from side effects after injection of Evolution is reported in the literature.

Teflon

Teflon is polytetrafluoroethylene paste. The histological aspect from a biopsy specimen is an extensive granulation tissue including lymphocytes and multinucleate giant cells surrounding a refractile foreign material.⁶⁷

Goretex

Goretex, expanded polytetrafluoroethylene, is presented as plaques, threads, or tubes of different diameters, which need to be implanted into the subcutis. Biopsy is taken from painful and partially ulcerated nodules. The threads are surrounded by accumulations of neutrophils, extravasated erythrocytes, and granulation tissue.⁴⁰

Conclusion

The use of filler injections, mainly for cosmetic reasons, will increase in the future and simultaneously, complications will probably be more frequent. An ideal filler still needs to be found. Moreover, unfortunately predictions cannot be made for possible late reactions. So the histological aspects of these side effects are important to know to identify the nature of the

responsible filler when clinical information is lacking or to confirm this clinical information if the patient takes legal action.

References

1. Clark DP, Hanke CW, Swanson NA: Dermal implants: safety of products injected for soft tissue augmentation. *J Am Acad Dermatol* 21(5 Pt. 1):992-998, 1989
2. Lemperle G, Hazan-Gauthier N, Lemperle M: PMMA microspheres (Artecoll) for skin and soft-tissue augmentation. Part II: Clinical investigations. *Plast Reconstr Surg* 96(3):627-634, 1995
3. Morgan AM: Localized reactions to injected therapeutic materials. Part 2. Surgical agents. *J Cutan Pathol* 22(4):289-303, 1995
4. Niechajev I: Lip enhancement: surgical alternatives and histologic aspects. *Plast Reconstr Surg* 105(3):1173-1183; discussion 1184-1187, 2000
5. Cheng JT, Perkins SW, Hamilton MM: Collagen and injectable fillers. *Otolaryngol Clin North Am* 35(1):73-85, 2002
6. Kligman AM, Armstrong RC: Histologic response to intradermal Zyderm and Zylplast (glutaraldehyde cross-linked) collagen in humans. *J Dermatol Surg Oncol* 12(4):351-357, 1986
7. Stegman SJ, Chu S, Bensch K, et al: A light and electron microscopic evaluation of Zyderm collagen and Zylplast implants in aging human facial skin. A pilot study. *Arch Dermatol* 123(12):1644-1649, 1987
8. Robinson JK, Hanke CW: Injectable collagen implant: histopathologic identification and longevity of the correction. *J Dermatol Surg Oncol* 11:124-130, 1985
9. Lemperle G, Morhenn V, Charrier U: Human histology and persistence of various injectable filler substances for soft tissue augmentation. *Aesthetic Plast Surg* 27(5):354-366, 2003; discussion 367
10. Burke KE, Naughton G, Cassai N: A histological, immunological, and electron microscopic study of bovine collagen implants in the human. *Ann Plast Surg* 14(6):515-522, 1985
11. Stegman SJ, Chu S, Armstrong R: Adverse reactions to bovine collagen implant: clinical and histologic features. *J Dermatol Surg Oncol* 14(Suppl. 1):39, 1988
12. Ackerman AB: *In Clues to Diagnosis in Dermatopathology II*. Chicago, IL: ASCP Press, 1992:386-387, 1992
13. Moscona RR, Bergman R, Friedman-Birnbaum R: An unusual late reaction to Zyderm I injections: a challenge for treatment. *Plast Reconstr Surg* 92(2):331-334, 1993
14. Constantinides M, Zimble MS, Jagirdar J: An unusual late reaction to facial injections. *Otolaryngol Head Neck Surg* 120(4):557-560, 1999
15. Rapaport MJ: Granuloma annulare caused by injectable collagen. *Arch Dermatol* 120(7):837-838, 1984
16. Guill MA, Goette DK: Granuloma annulare at sites of healing herpes zoster. *Arch Dermatol* 114(9):1383, 1978
17. Muhlbauer JE: Granuloma annulare. *J Am Acad Dermatol* 3:217-230, 1980
18. Hanke CW, Higley HR, Jolivet DM, et al: Abscess formation and local necrosis after treatment with Zyderm or Zylplast collagen implant. *J Am Acad Dermatol* 25(2 Pt. 1):319-326, 1991
19. Hexsel DM, Hexsel CL, Iyengar V: Liquid injectable silicone: history, mechanism of action, indications, technique, and complications. *Semin Cutan Med Surg* 22(2):107-114, 2003
20. Sclafani A, Romo T, Jacono A, et al: Evaluation of acellular dermal graft in sheet (Alloderm) and injectable (micronized Alloderm) forms for soft tissue augmentation: clinical observations and histologic findings. *Arch Facial Plast Surg* 2:48-52, 2000
21. Duranti F, Salti G, Bovani B, et al: Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histological study. *Dermatol Surg* 24(12):1317-1325, 1998
22. Piacquadro D, Jarcho M, Goltz R: Evaluation of hylan b gel as a soft-tissue augmentation implant material. *J Am Acad Dermatol* 36(4):544-549, 1997
23. Micheels P: Human anti-hyaluronic acid antibodies: is it possible? *Dermatol Surg* 27(2):185-191, 2001
24. Fernandez-Acenero MJ, Zamora E, Borbujo J: Granulomatous foreign

- body reaction against hyaluronic acid: report of a case after lip augmentation. *Dermatol Surg* 29(12):1225-1226, 2003
25. Lowe NJ, Maxwell CA, Lowe P, et al: Hyaluronic acid skin fillers: adverse reactions and skin testing. *J Am Acad Dermatol* 45(6):930-933, 2001
 26. Shafir R, Amir A, Gur E: Long-term complications of facial injections with Restylane (injectable hyaluronic acid). *Plast Reconstr Surg* 106(5):1215-1216, 2000
 27. Honig JF, Brink U, Korabiowska M: Severe granulomatous allergic tissue reaction after hyaluronic acid injection in the treatment of facial lines and its surgical correction. *J Craniofac Surg* 14(2):197-200, 2003
 28. Schanz S, Schippert W, Ulmer A, et al: Arterial embolization caused by injection of hyaluronic acid (Restylane). *Br J Dermatol* 146(5):928-929, 2002
 29. Friedman PM, Mafong EA, Kauvar AN, et al: Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg* 28(6):491-494, 2002
 30. Lowe NJ: Arterial embolization caused by injection of hyaluronic acid (Restylane). *Br J Dermatol* 148(2):379, 2003; author reply 379-380
 31. Rongioletti F, Cattarini G, Sottofattori E, et al: Granulomatous reaction after intradermal injections of hyaluronic acid gel. *Arch Dermatol* 139(6):815-816, 2003
 32. Lombardi T, Samson J, Plantier F, et al: Orofacial granulomas after injection of cosmetic fillers. Histopathologic and clinical study of 11 cases. *J Oral Pathol Med* 33(2):115-120, 2004
 33. Lemperle G, Ott H, Charrier U, et al: PMMA microspheres for intradermal implantation: Part I. Animal research. *Ann Plast Surg* 26(1):57-63, 1991
 34. McClelland M, Egbert B, Hanko V, et al: Evaluation of Artecoll polymethylmethacrylate implant for soft-tissue augmentation: biocompatibility and chemical characterization. *Plast Reconstr Surg* 100(6):1466-1474, 1997
 35. Pollack S: Some new injectable dermal filler materials: Hylaform, Restylane, and Artecoll. *J Cutan Med Surg* 3(Suppl. 4):S27-35, 1999
 36. Lemperle G, Gauthier-Hazan N, Lemperle M: PMMA-Microspheres (Artecoll) for long-lasting correction of wrinkles: refinements and statistical results. *Aesthetic Plast Surg* 22(5):356-365, 1998
 37. Lemperle G, Romano JJ, Busso M: Soft tissue augmentation with Artecoll: 10-year history, indications, techniques, and complications. *Dermatol Surg* 29(6):573-587, 2003; discussion 587
 38. Rudolph CM, Soyer HP, Schuller-Petrovic S, et al: Foreign body granulomas due to injectable aesthetic microimplants. *Am J Surg Pathol* 23(1):113-117, 1999
 39. Mang WL, Sawatzaki K: Fremdkörperreaktion nach Implantation von PMMA (Polymethylmethacrylat) zur Weichteilaugmentation. *Z Hautkrankh* 73:42-44, 1998
 40. Hoffmann C, Schuller-Petrovic S, Soyer HP, et al: Adverse reactions after cosmetic lip augmentation with permanent biologically inert implant materials. *J Am Acad Dermatol* 40(1):100-102, 1999
 41. Requena C, Izquierdo MJ, Navarro M, et al: Adverse reactions to injectable aesthetic microimplants. *Am J Dermatopathol* 23(3):197-202, 2001
 42. Reisberger EM, Landthaler M, Wiest L, et al: Foreign body granulomas caused by polymethylmethacrylate microspheres: successful treatment with allopurinol. *Arch Dermatol* 139(1):17-20, 2003
 43. Alcalay J, Alcalay R, Gat A, et al: Late-onset granulomatous reaction to Artecoll. *Dermatol Surg* 29(8):859-862, 2003
 44. Kim KJ, Lee HW, Lee MW, et al: Artecoll granuloma: a rare adverse reaction induced by microimplant in the treatment of neck wrinkles. *Dermatol Surg* 30(4 Pt. 1):545-547, 2004
 45. Bergeret-Galley C, Latouche X, Illouz YG: The value of a new filler material in corrective and cosmetic surgery: DermaLive and DermaDeep. *Aesthetic Plast Surg* 25(4):249-255, 2001
 46. Travis WD, Balogh K, Abraham JL: Silicone granulomas: report of three cases and review of the literature. *Hum Pathol* 16(1):19-27, 1985
 47. 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* 94(1):65-73, 2002
 48. Bigata X, Ribera M, Bielsa I, et al: Adverse granulomatous reaction after cosmetic dermal silicone injection. *Dermatol Surg* 27(2):198-200, 2001
 49. Hexsel DM, Hexsel CL, Iyengar V: Liquid injectable silicone: history, mechanism of action, indications, technique, and complications. *Semin Cutan Med Surg* 22(2):107-114, 2003
 50. Senet P, Bachelez H, Ollivaud L, et al: Minocycline for the treatment of cutaneous silicone granulomas. *Br J Dermatol* 140(5):985-1004, 1999
 51. Rapaport MJ, Vinnik C, Zarem H: Injectable silicone: cause of facial nodules, cellulitis, ulceration, and migration. *Aesthetic Plast Surg* 20(3):267-276, 1996
 52. Faure M: Complications from silicone implants and other so-called inert materials. *Ann Dermatol Venerol* 122(6-7):455-459, 1995
 53. Ackerman AB: *In Clues to Diagnosis in Dermatopathology I*. Chicago, IL: ASCP Press, 394-395, 1990
 54. Mastruserio DN, Pesqueira MJ, Cobb MW: Severe granulomatous reaction and facial ulceration occurring after subcutaneous silicone injection. *J Am Acad Dermatol* 34(5 Pt. 1):849-852, 1996
 55. Schmidt-Westhausen AM, Frege J, Reichart PA: Abscess formation after lip augmentation with silicone: case report. *Int J Oral Maxillofac Surg* 33(2):198-200, 2004
 56. Pimentel L, Barnadas M, Vidal D, et al: Simultaneous presentation of silicone and silica granuloma: a case report. *Dermatology* 205(2):162-165, 2002
 57. Weiss SW, Goldblum JR: *Liposarcoma: In Enzinger and Weiss's Soft Tissue Tumors*, fourth ed. St. Louis, MO: Mosby, 642-645, 2001
 58. Maly A, Regev E, Meir K, et al: Tissue reaction to liquid silicone simulating low-grade liposarcoma following lip augmentation. *J Oral Pathol Med* 33(5):314, 2004
 59. Allen O: Response to subdermal implantation of textured microimplants in humans. *Aesthetic Plast Surg* 16(3):227-230, 1992
 60. Rudolph CM, Soyer HP, Schuller-Petrovic S, et al: Bioplastique granuloma. *Hautarzt* 48(10):749-752, 1997
 61. Simons G, Mazaleyrat P, Masurel T: Utilization of injectable microimplants in aesthetic facial surgery. *Aesthetic Plast Surg* 16(1):77-82, 1992
 62. Beisang AA 3rd, Ersek RA: Mammalian response to subdermal implantation of textured microimplants. *Aesthetic Plast Surg* 16(1):83-90, 1992
 63. Ersek RA, Beisang AA 3rd: Bioplastique: a new biphasic polymer for minimally invasive injection implantation. *Aesthetic Plast Surg* 16(1):59-65, 1992
 64. Ersek RA, Beisang AA 3rd: Bioplastique: a new textured copolymer microparticle promises permanence in soft-tissue augmentation. *Plast Reconstr Surg* 87(4):693-702, 1991
 65. Klein JA, Cole G, Barr RJ, et al: Paraffinomas of the scalp. *Arch Dermatol* 121(3):382-385, 1985
 66. Morgan AM: Localized reactions to injected therapeutic materials. Part I. Medical agents. *J Cutan Pathol* 22(3):193-214, 1995
 67. Maas CS, Papel ID, Greene D, et al: Complications of injectable synthetic polymers in facial augmentation. *Dermatol Surg* 23(10):871-87, 1997
 68. de Cassia Novaes W, Berg A: Experiences with a new nonbiodegradable hydrogel (Aquamid): a pilot study. *Aesthetic Plast Surg* 27(5):376-380, 2003
 69. de Bree R, Middelweerd MJ, van der Waal I: Severe granulomatous inflammatory response induced by injection of polyacrylamide gel into the facial tissue. *Arch Facial Plast Surg* 6(3):204-206, 2004