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Adverse Results with PMMA Fillers

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Abstract
Background Various alloplastic materials have been used for filling depressions and for body contouring. Among them, polymethylmethacrylate (PMMA) has provoked many clinical compilations in both the acute and chronic phases. This study shows the correlation between the clinical application of PMMA and the physiopathology of the acute and late complications.
Methods Histological studies were performed on biopsy samples from patients who presented with side effects and acute and late complications after PMMA injections given at other health-care centers or aesthetic services.
Results The histological findings of the samples that were harvested from patients who developed clinical complications or side effects caused by injection of PMMA disclosed not only normal tissues from the implanted areas but also development of capsules that involved individual microspheres of PMMA, and when the capsules were close together they formed concentric capsular groups involving various sets of microspheres and their capsules.
Conclusions The injection of PMMA within the tissues can cause severe complications and side effects in both acute and chronic phases. Initially, the complications are related to vascular compromise, but at the late phase they are a consequence of capsular contracture that involves particles of PMMA. The contracture causes local tissue hardening and clinical nodulation of the implanted areas, ending with extrusion of the filler material.
Level of Evidence IV This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors at www.springer.com/00266.

Keywords Polymethylmethacrylate · Adverse results · Complications with PMMA

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In the search for better definition in body contouring, fillers with alloplastic substances [1–5] or transplants of autologous tissues [6, 7] have been used for filling depressions. The alloplastic materials used for these corrections are divided into two groups: the absorbable or biodegradable type such as hyaluronic acid [8, 9], and those endowed with a plastic component. As these are not absorbable or biodegradable, they remain inside the tissues for a long time. With the use of these substances in humans, complications have been reported in both the acute and chronic phases. Within this group of fillers are polymethylmethacrylate (PMMA), known as acrylic, and polymethylsiloxane (DMS), known as silicone [10–34].

PMMA, a thermolabile plastic material, is synthesized from the polymerization of its monomer: ester methyl methylpropenoate ($C_5O_2H_8$). For filling depressions and for body contouring, PMMA is commercially available as an injectable not only as gel but also as microspheres, in which the PMMA is made up of a solid fraction and a biodegradable colloid vehicle. The solid fraction is composed of nondegradable acrylic microspheres with diameters reaching 80 μm [34].

The aim of the present work is to analyze the correlation between the use of PMMA microspheres for filling depressions and body contouring and clinical complications. Moreover, in confirmed cases we searched for a correlation between the histological findings of the samples

that were harvested from the patients and the physiopathology of the adverse results, in both the acute and chronic phases.

Method

We performed a retrospective study by reviewing the medical records of 96 patients who had any complaint after injection of an alloplastic substance for filling depressions in body contours. All of them were first treated at other services, and because those services did not have a database with patient information, it was not possible to obtain important information such as substances' characteristics, volume used, regions filled, and time it took for the complications to appear.

Through information obtained from patients and from the biopsy's histologic results and surgical extirpations, it was possible to find that 63 of them had received PMMA microspheres and no one was immunocompromised or carried any degenerative disease. Among these patients, three had acute complications, two had cicatricial deformities with more than 3 years of evolution as a consequence of acute complications, and 58 had late complications. In the latter group, the product had been previously implanted between 6 months and 10 years, and, when checked, all of them had hardened nodules (local tissue hardening and clinical nodulation) at the region of the PMMA implant. Also, eight had abscesses in the compromised area.

Among the 63 who had received PMMA filler, 48 underwent some type of surgical treatment and the material obtained was subjected to histopathologic examination. Furthermore, with the data on the clinical history, a chronological mapping of the complications' evolution was assembled. Finally, the histological findings were correlated with the clinical aspects of the lesions and a hypothesis that explains the physiopathology of the acute and chronic complications of the use of PMMA microspheres was formulated.

Results

Inflammatory Reaction to PMMA

Once injected inside the tissues as thousands of microimplants, the PMMA triggers a granulomatous inflammatory reaction with different characteristics in the acute and chronic phases. The material obtained from the lesion with 30 days of evolution was characterized by the presence of inflammatory aspects of an acute lesion. This reaction presented as a cellular infiltrate composed mainly of neutrophils, lymphocytes, macrophages, and cells similar to fibroblasts. Moreover, two types of empty space were observed: the smallest with a round shape, and the largest with an irregular shape. These empty spaces are suggestive of the presence of PMMA microspheres and of the vehicle not yet reabsorbed; in this phase, they were interwoven within irregular and loose connective tissue (Fig. 1).

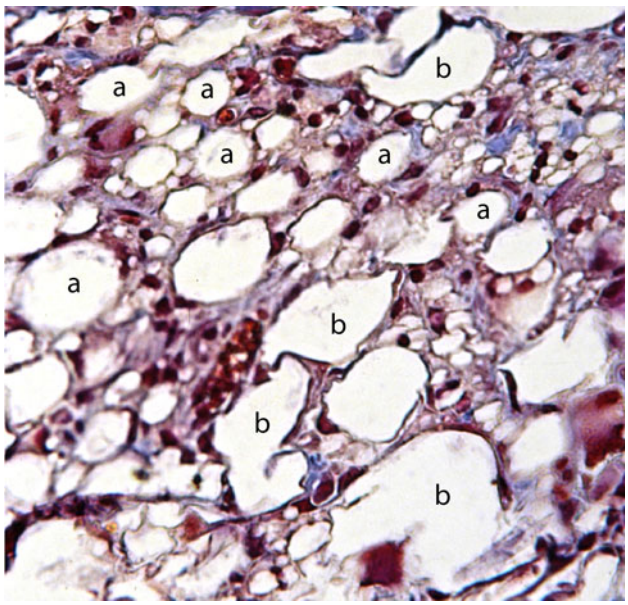

Fig. 1 Inflammatory aspect of the reaction to PMMA with 30 days of evolution. Inflammatory cells are noticed and (*a*) smaller round empty spaces that were formed by the presence of microspheres, and (*b*) bigger irregular empty spaces that were formed by the presence of the vehicle not yet absorbed (Trichromic ×40)

The tissues obtained from the lesions with 6 months or more of evolution had inflammatory characteristics different from the tissues described above and, therefore, were characterized as late lesions. The histopathologic exam of this material showed the presence of small and round empty spaces surrounded by dense and organized inflammatory tissue. These spaces were probably occupied by the microspheres that were dislodged in the preparation of the material (Figs. 2, 3, 4, 5).

There are two things noteworthy about the chronic inflammatory reaction around the PMMA spheres: one with respect to the reaction around each microsphere, and one with respect to the group. An individual inflammatory process in reaction to the microspheres was observed, where in the inner portion of these empty spaces, in direct contact with the PMMA, cells similar to macrophages that were juxtaposed creating gigantic cells were observed. Moreover, in the outer part there was collagen tissue aligned with a circular shape that was rich in fine blood vessels and generated a chronic inflammatory reaction, typical of a foreign body reaction (Fig. 5).

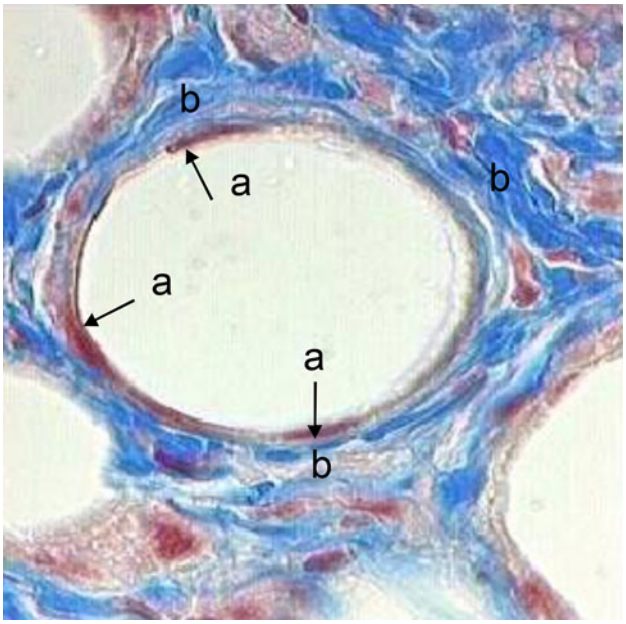

Fig. 2 Photomicrograph showing an inflammatory reaction with 2 years of evolution, where round empty spaces involved by a foreign body inflammatory reaction type are observed. In the internal region there are some macrophage-like cells (*a*). In the outer part one surrounding capsule (*b*) (Trichromic ×400)

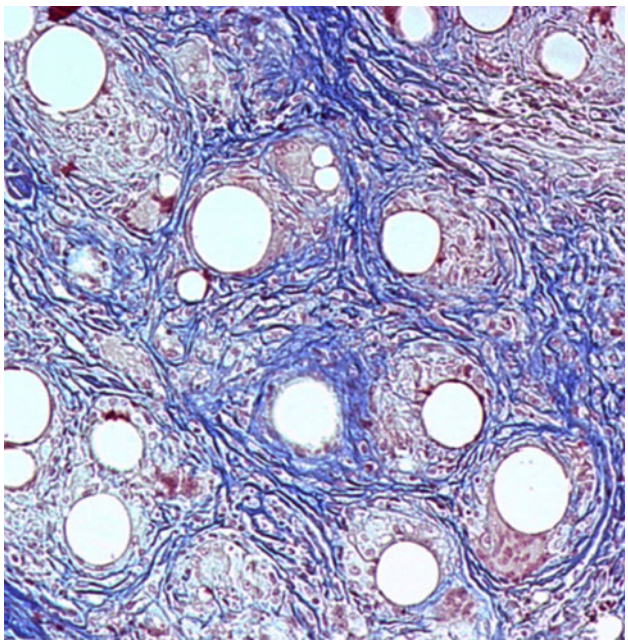

Fig. 3 Photomicrograph indicating the detail of the reaction to PMMA. Observe the capsules involving empty spaces with groups of two, three, and four microspheres (Trichromic ×100)

With a wider view of the inflammatory reaction to the implanted material, it was observed that the concentration (amount and distance) of the microspheres was a determining factor in the capsule organization of the inflammatory process as a whole. When distant from each other,

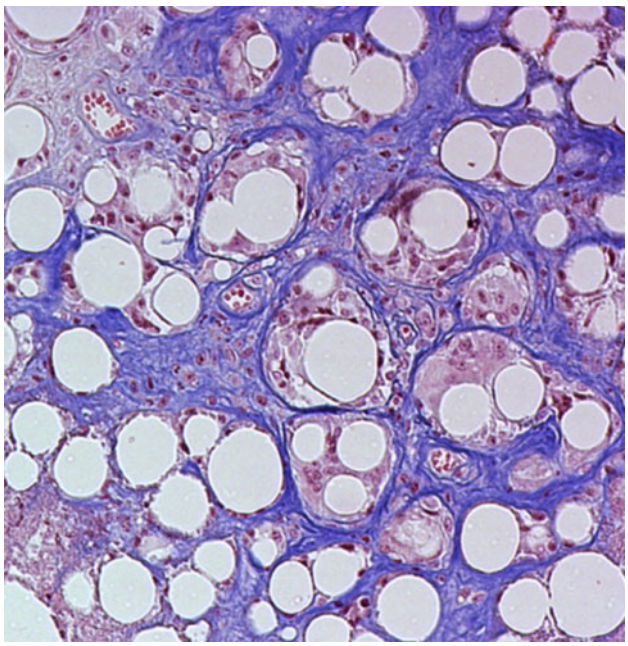

Fig. 4 Photomicrograph showing an inflammatory reaction with capsular tissue involving several microspheres (Trichromic ×60)

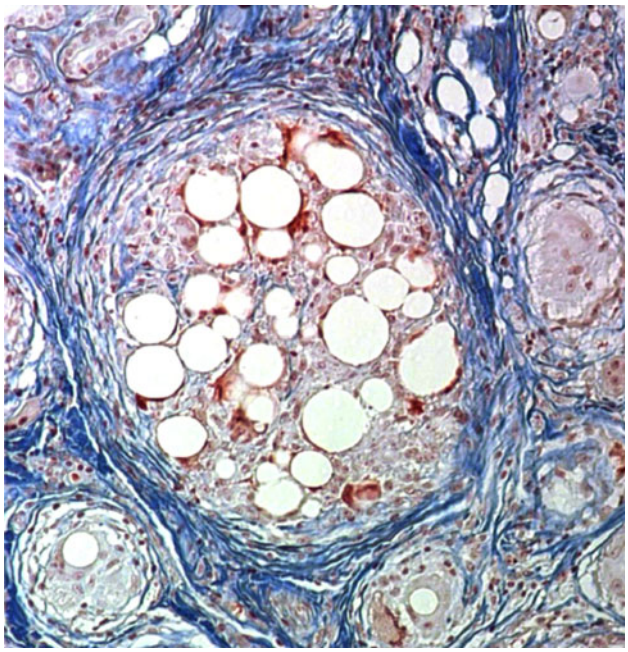

Fig. 5 Photomicrograph revealing the detail of the reaction to PMMA. Notice that the microspheres' empty spaces are separated, forming individual capsular reactions (Trichromic ×100)

the microspheres produce isolated capsule units (Fig. 2), and when close to each other—enough so that their inflammatory tissues overlap—they distribute themselves into groups of capsules with their different amounts of microspheres and their individual inflammatory reactions (Figs. 3, 4). Furthermore, these groups of microspheres end

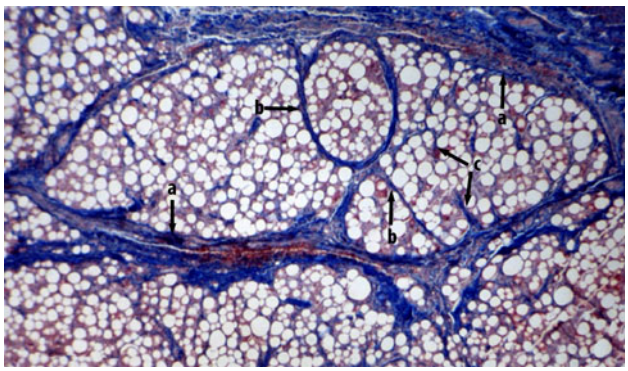

Fig. 6 Photomicrograph revealing details of concentric capsules. The outer capsules (*a*) are thicker than the inner capsules (*b*). Inner capsules being absorbed (*c*) (Trichromic ×25)

up being involved by outer capsules, thus creating concentric capsular groups in which the outer capsules are thicker than the inner ones (Fig. 5). It was still possible to observe that in these cases there was a higher density of microspheres (Fig. 6).

Another aspect that deserves attention is the presence of normal excised tissues such as fat, vessels, muscles, cartilage and nerves together with the PMMA inflammatory process. In the surgical resection of the inflammatory nodules there are also lesions of the local tissues (Figs. 7, 8, 9).

Clinical Complications with the Use of PMMA

The clinical complications from PMMA injections were divided into two groups: acute and chronic. The five patients who had suffered acute complications had tissue necrosis after the injection; they also reported that the problem started during the injection when they felt an intense pain that remained during the first few days afterward. During this period, the skin of the compromised area changed color from whitish to violet and finally became necrotic. In these patients, two different aspects were observed regarding the compromised area: necrosis that remained restricted to the areas where the material was injected (Figs. 10, 11), and distant areas where the compromised area corresponded to the region nurtured by an artery (Figs. 12, 13).

The late complications were observed from the sixth postprocedure month, and in all the patients a similar clinical evolution was noticed that may be sequenced and graduated. The complaints started with the description of a palpable mass in the place where the PMMA was injected. This mass was slightly hardened with a flat touchable form but it not visible. A second group of patients experienced touchable, round, and harder nodules which, in the face region, became externally visible in the skin or mucosa,

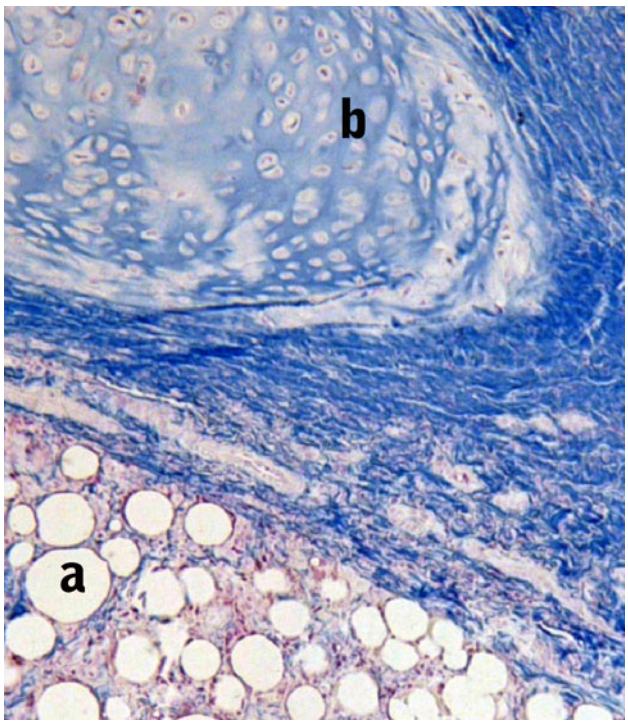

Fig. 7 Granulomatous tissue taken from nasal columella. Besides the empty spaces to PMMA (*a*), a cartilage fragment is observed (*b*) (Trichromic ×60)

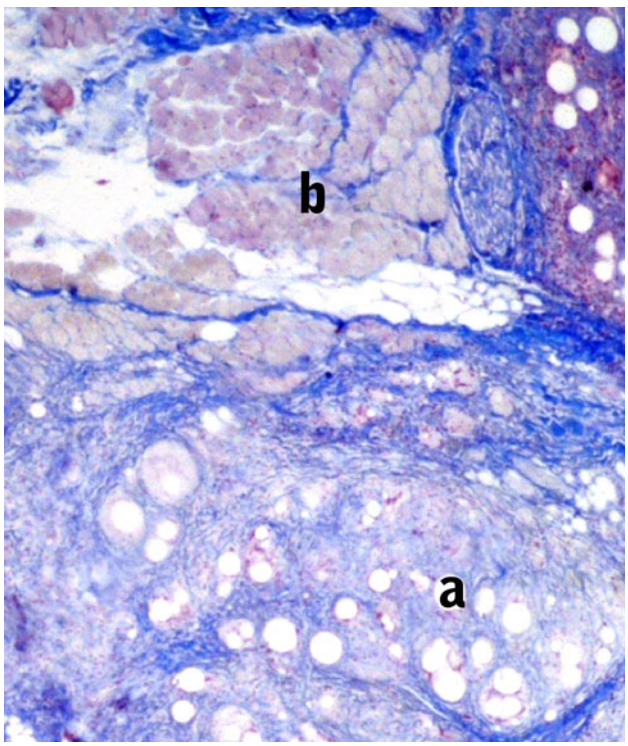

Fig. 8 Photomicrograph of granulomatous tissue taken from the cheek area. Besides the reaction to PMMA (*a*), the presence of muscle is noted (*b*) (Trichromic ×40)

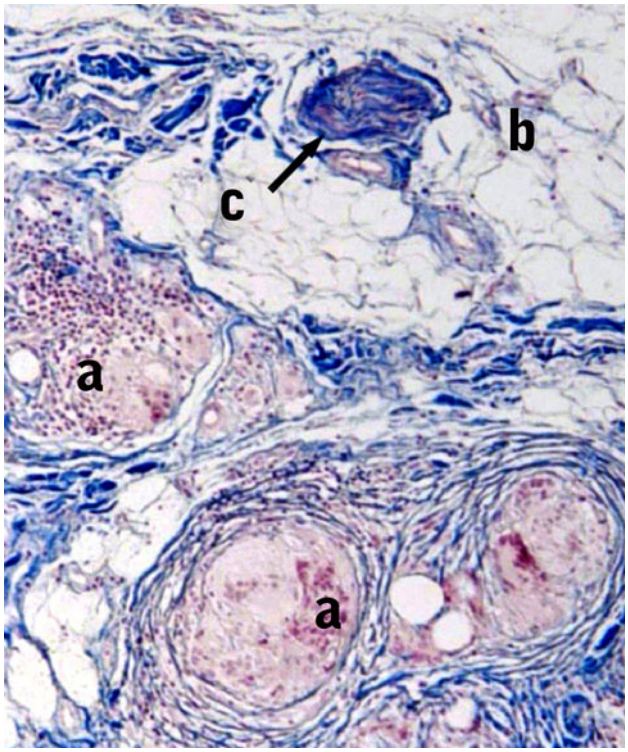

Fig. 9 Granulomatous tissue taken from the cheek area Besides the reaction to PMMA (*a*), the presence of fat (*b*) and nerve (*c*) are observed (Trichromic ×40)

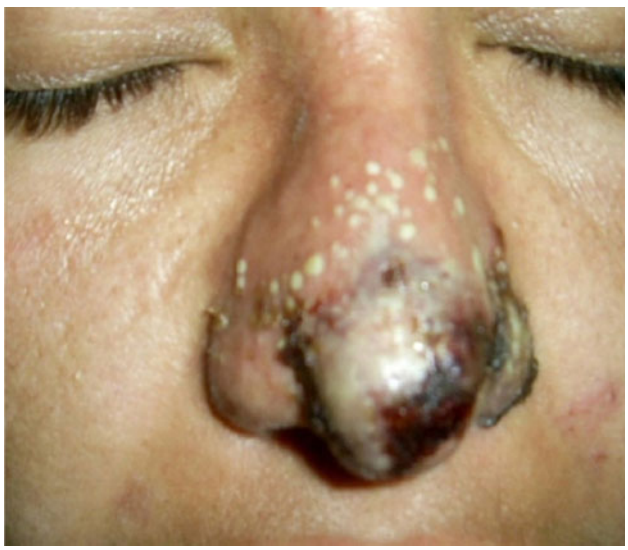

Fig. 10 Necrosis of the tip of the nose region with 10 days of evolution after filling with PMMA

and they complained about some aesthetic and/or functional compromise. Complaints also included edema, pruritus, mimicry alteration, volume increase of the compromised area, bite (when in the oral mucosa), and pain while sitting (when in the gluteal region) (Figs. 14, 15, 16). A third group of patients had the same complaints as

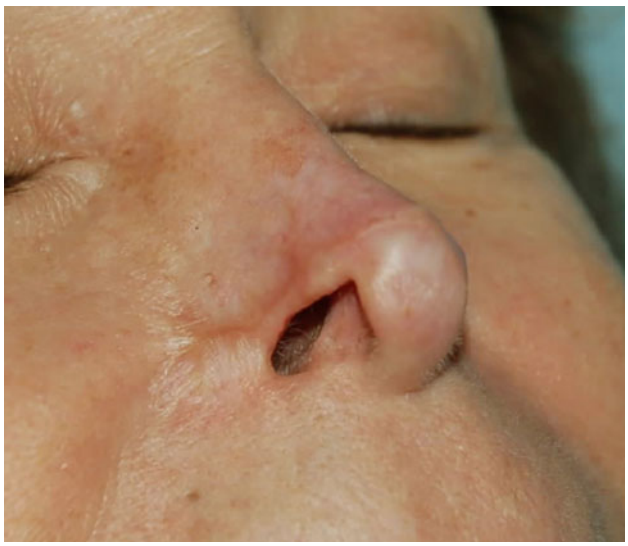

Fig. 11 Cicatricial aspect of the nasal region after an acute complication as a consequence of filling with PMMA, 2 years of evolution

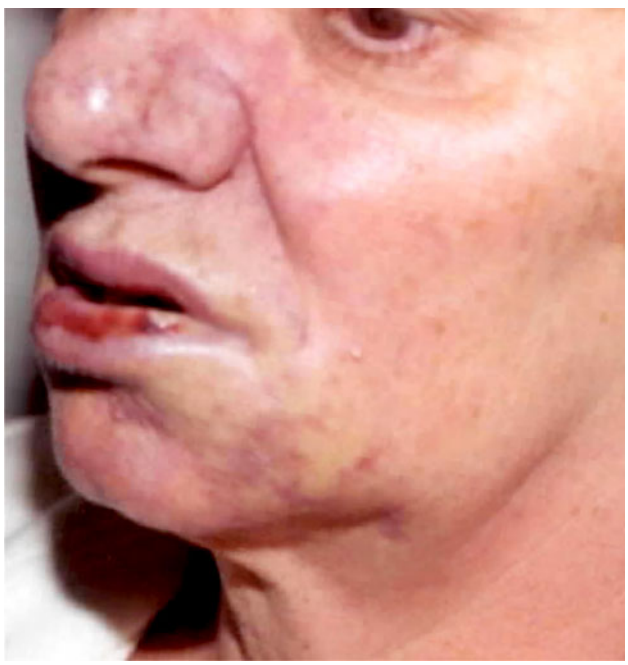

Fig. 12 Violet region 3 days after PMMA injection

the other groups but also had round and well-hardened nodules that when in contact with the skin, caused a projection and the region showed itself compromised, i.e., hyperemic and sometimes with telangiectasia of the subdermal vessels (Fig. 17). Finally, apart from the previous alterations, eight patients had microabscesses in the compromised region, and, most importantly, they reported an evolution of the complications that was similar to that of the previous groups until the appearance of the cutaneous lesions (Fig. 18).

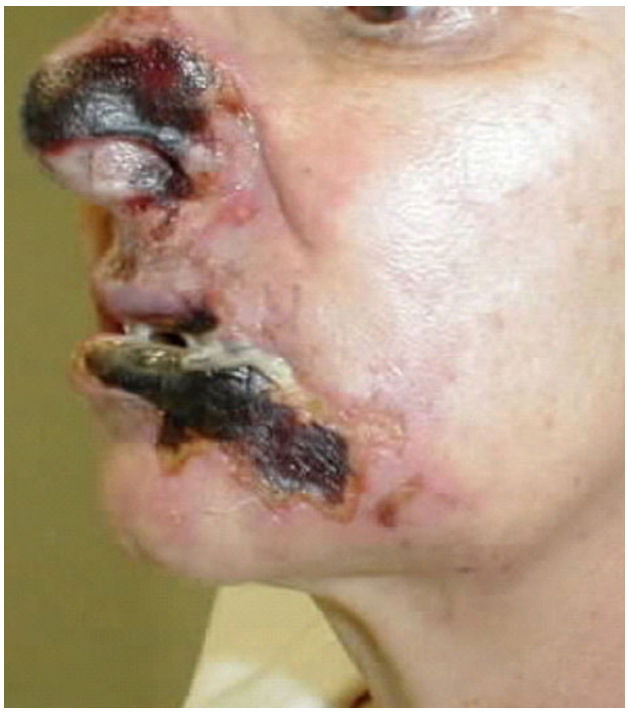

Fig. 13 Necrosis of the nasolabial region 20 days after PMMA injection

Fig. 14 Gingival mucosa showing intraoral projections of PMMA, after 6 months of evolution

Of the 58 patients who presented late complications, seven were treated with intralesional corticosteroid injection. These patients reported an initial recovery with the

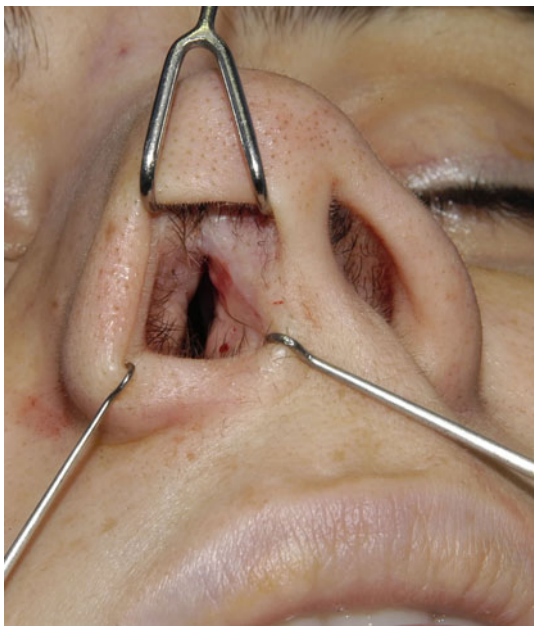

Fig. 15 Nasal valve stenoses 15 months after PMMA injection

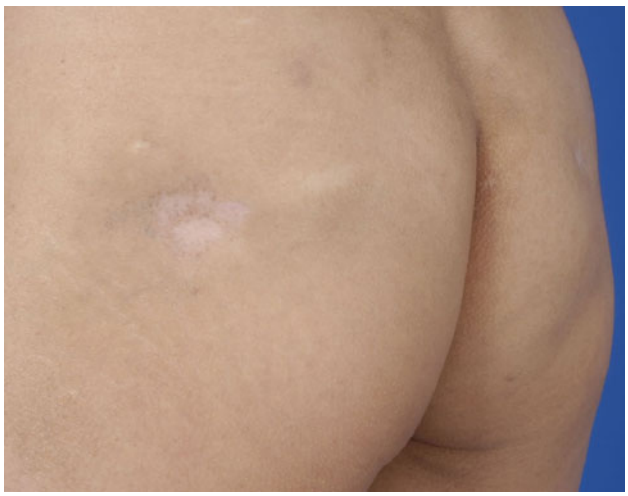

Fig. 16 Hardened nodules of the gluteal region 18 months after injection of PMMA. Depressions and depigmentation after corticoid injection are also noted

softening of the compromised region but after a few months the nodule became harder and the skin of the region where the product had been injected turned whitish and depressed (Figs. 16, 19).

Discussion

The clinical use of injectable PMMA in the form of microspheres has generated complications in both acute and late phases [28–34]. The 96 patients reviewed in this study were initially seen at other services where they had

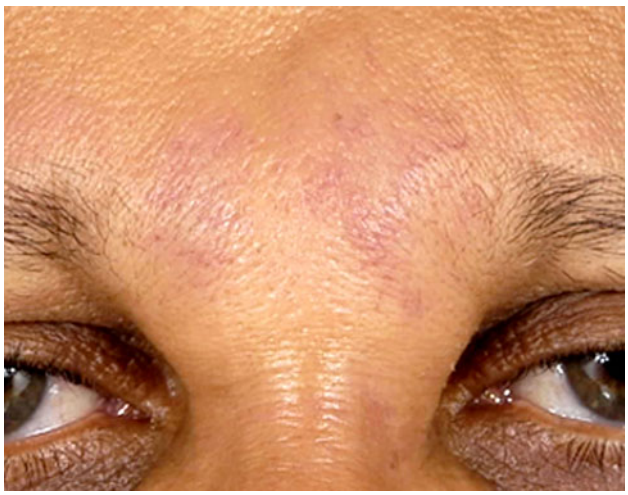

Fig. 17 Patients with visible nodules in the skin after filling with PMMA with evolution of more than 2 years. In the nodule region the skin is hyperemic and with telangiectasia

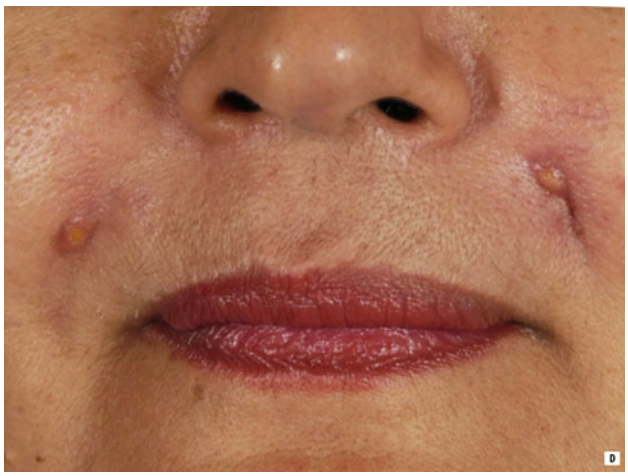

Fig. 18 Abscesses in the nasolabial fold region 4.5 years after filling with PMMA. The wounds have been open for 13 months

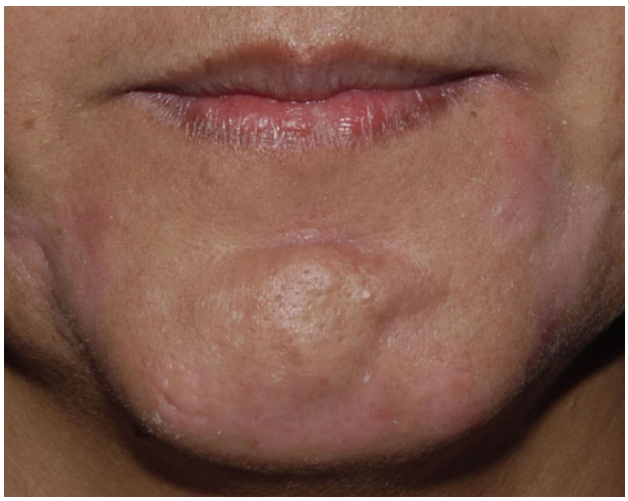

Fig. 19 Atrophy and depigmentation of the chin after corticosteroid injection

injections of alloplastic substances as fillers. The lack of data on the technical and surgical aspects of the treatments prevented us from analyzing some important data such as product origin, amount injected, anatomic plane filled, number of patients initially treated, total number of patients with complications, and evolution periods of time. Despite this, it was possible to observe several important points that probably are directly related to the number and time of appearance of complications. These include at least seven factors: physical and chemical characteristics of the substance and of the vehicle, amount of product, concentration and size of the microspheres, tissue filled, and aspects of each patient's inflammatory response.

Because of the several factors involved and the lack of information from before the complications, the time between product injection and the appearance of complications and the relationship between the number of complications and the patients treated were not assessed in this work.

Of the 63 patients studied in this work, five had severe complications in the acute stage with tissue necrosis. In the case of necrosis, two different types were observed: one where the necrosis remained confined to the infiltrated region (Figs. 10, 11), and the other where compromised tissues appeared away from the injection site (Figs. 12, 13). In both cases a similar clinical evolution was noted. The patients reported intense pain during the injection, which remained through the first few days after the procedure. In addition, there was a change in skin color that started during the PMMA injection, going from whitish to violet, and after 3 days there were signs of necrosis (Figs. 12, 13). From the clinical characteristics of the acute complications in the compromised region, it is possible to conclude that they were related to vascular alterations. In the case of local necrosis, the PMMA was injected in the tip of the nose over hard structures. This led to a displacement of the superficial tissues, with distention, vascular compression, and, consequently, compromise of the tissues' local nutrition (Figs. 10, 11). In the case of distant complications, the physiopathology of the necrosis is explained by intravascular injection of the microspheres with consequent embolization and compromise of the tissues nourished by the compromised vascular branch (Figs. 12, 13).

The 58 patients who said their complications appeared between 6 months and 10 years after the injection of PMMA were grouped as late complications. These chronic alterations occurred where the product was found; this was proved by the histopathological examination of the obtained material. The late lesions followed a similar and gradual sequence in their clinical aspects; thus, they were classified into four levels, as was the functional-aesthetic commitment of the compromised area:

- Level 1: ellipsoid nodule, slightly hardened and touchable, not visible, and without functional complaints.
- Level 2: round and consistent nodule which when near the surface projects volume in the mucosa or in the skin causing functional-aesthetic disorders, depending on the compromised region (Figs. 14, 15, 16).
- Level 3: round and hard nodule which when near the cutaneous/mucosal surface, besides the projection that makes the nodule visible, makes the region of the compromised skin hyperemic and sometimes with telangiectasia, provoking functional-aesthetic disturbances (Fig. 17).
- Level 4: round and hard nodule with functional-aesthetic disturbances of the region and abscess in the compromised skin (Fig. 18).

The evolution and appearance of the late lesions previously cited may be explained by the presence of nondegradable plastic microspheres inside the tissues. This triggers a granulomatous inflammatory reaction, typical of foreign bodies. This reaction ends up involving the material within a collagenous capsule. These reactions are well known with silicone breast implants and may in the chronic phase evolve with contracture [35]. This phenomenon also seems to occur with PMMA fillers for body contouring. In this case, the inflammatory reaction has its own features in that besides capsules occurring individually around each sphere there is also the formation of concentric capsules involving different groups of microspheres (Figs. 2, 3, 4, 5, 6). Histological study of these reactions reveals that the outer capsules are thicker than the inner ones. This probably makes them more effective in the isolation of the implanted material and in the contracture (Fig. 6). Therefore, in the chronic phase of the granulomatous process, which may take years, a decrease in the inducement of inner inflammation occurs while the outer capsule remodels and contracts itself. Consequently, the microspheres, in a dynamic process, tend to approach each other, leading to the late hardening of the granulomatous nodule that matches the beginning of the clinical complaints. From this phase, the body has nonspecific inflammatory mechanisms that may evolve with the formation of abscesses in order to extrude the implanted material (Fig. 18).

The formation of abscesses in the skin has inherent aspects in this type of filling because inside the tissues the microspheres cluster themselves in various capsular groups, unequal in size, shape, and deepness (Fig. 20), which explains the occurrence of cyclical periods of variable lengths of time, when abscesses and wound closure alternate.

The clinical treatment proposed for late complications—antibiotic therapy and corticosteroid injection—is ineffective because it does not treat the causes but the consequences. This is because the infections are secondary to the extrusion process: the immunosuppression only temporarily inhibits the inflammatory reaction. Moreover, corticosteroid injection in the inner section of the granulomatous tissue initially softens the inflammatory nodule. However, over time, the injection triggers harmful effects to the organism as the corticosteroid leads to absorption of the inner collagen, enabling the microspheres to approach each other by the contraction of the outer capsule, causing, within a short period of time, an even greater hardening of the granulomatous tissue. In addition, the corticosteroid usually extravasates the nodule region and reaches the neighboring tissues, producing two other important local changes. In normal tissues, the corticosteroid's action produces atrophy with consequent local depression and greater exposure of the hardened granulomatous nodule, and when it reaches the skin, it leads to atrophy of the dermis with epidermis depigmentation. Thus, the cutaneous visualization of the subdermal vascular plexus occurs (Figs. 16, 19). Thus, the use of corticosteroid for the treatment of the granulomatous nodule, induced by the presence of the acrylic microspheres, results in even more deterioration of the functional-aesthetic alterations of the compromised regions.

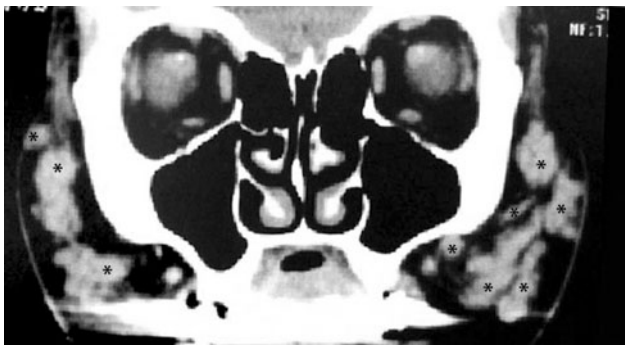

Fig. 20 View from a tomographic cut where whitish regions *asterisk* due to filling with PMMA are observed

The only treatment that is effective for patients who present the complications cited is the surgical removal of the product. Nevertheless, as the injection of microspheres inside the tissues compromises vessels, nerves, muscles, cartilage, and fat, this removal results in scars, depressions, and also possible lesions of normal tissues (Figs. 7, 8, 9, 20).

Conclusion

PMMA injection for correcting body contours may present overall good results initially; however, in many cases it may trigger severe acute and chronic complications. The acute complications are related to vascular compromise

and the chronic complications are related to an inflammatory process that, in the late phase, produces hardened nodules, a consequence of the capsular contracture that involves the material. Such contracture may lead to deformity, functional-aesthetic compromise, and chronic abscesses. The late complications, difficult to treat, almost always leave sequelae. Therefore, the use of this product must be indicated only with restrictions.

Conflict of interest The authors have no conflicts of interest to disclose.

References

1. Habal MB (1984) The biologic basis for the clinical application of the silicones. A correlate to their biocompatibility. Arch Surg 119(7):843–848
2. Hotta T (2004) Dermal fillers. The next generation. Plast Surg Nurs 24(1):14–19
3. Lemperle G, Morhenn V, Charrier U (2003) Human histology and persistence of various injectable filler substances for soft tissue augmentation. Aesthet Plast Surg 27(5):354–366
4. Lemperle G, Gauthier-Hazan N, Lemperle M (1998) PMMA-microspheres (Artecoll) for long-lasting correction of wrinkles: refinements and statistical results. Aesthet Plast Surg 22(5):356–365
5. Rosa SC, Soares de Macedo JL (2007) Injectable materials for soft tissue augmentation. Rev Soc Bras Cir Plást 22(2):116–121
6. Carpaneda CA (2006) Lipoinjertos. En: Coiffman F (ed), Cirurgia plástica, reconstructiva y estética. Capítulo 50. Tomo I, pp 476–486
7. Coleman SR (2006) Structural fat grafting: more than a permanent filler. Plast Reconstr Surg 118(Suppl 3):108S–120S
8. Duranti F, Satti G, Bovani B, Calandra M, Rosati ML (1998) Injectable hyaluronic acid gel for soft tissue augmentation: a clinical and histological study. Dermatol Surg 24(3):1317–1325
9. Olenius M (1998) The first clinical study using a new biodegradable implant for the treatment of lips, wrinkles and folds. Aesthet Plast Surg 22(2):97–101
10. Rapaport MJ, Vinnik C, Zarem H (1996) Injectable silicone: cause of facial nodules, cellulites, ulceration and migration. Aesthet Plast Surg 20:267–276
11. Requena C, Izquierdo MJ, Navarro M et al (2001) Adverse reactions to injectable aesthetic microimplants. Am J Dermatopathol 23:197–202
12. Senet P, Bachelez H, Ollivaud L, Vignon-Pennamen D, Dubertret L (1999) Microcycline for the treatment of cutaneous silicone granulomas. Br J Dermatol 140:985–987
13. Manafi A, Emami AH, Pooli AH, Habibi M, Saidian L (2010) Unacceptable results with an accepted soft tissue filler: polyacrylamide hydrogel. Aesthet Plast Surg 34:413–422
14. Zimmermann US, Clerici TJ (2004) The histological aspects of fillers complications. Semin Cutan Med Surg 23(4):241–250
15. Andre P, Lowe NJ, Parc A, Clerici TH, Zimmermann U (2005) Adverse reactions to dermal fillers: a review of European experiences. J Cosmet Laser Ther 7(3–4):171–176
16. Bigata X, Ribera M, Bielsa I, Ferrandiz C (2001) Adverse granulomatous reaction after cosmetic dermal silicone injection. Dermatol Surg 27:198–200
17. Breiting V, Aasted A, Jorgensen A et al (2004) A study on patients treated with polyacrylamide hydrogel injection for facial corrections. Aesthet Plast Surg 28:45–53
18. Cheng N, Wang Y, Wang J et al (2002) Complications of breast augmentation with injected hydrophilic polyacrylamide gel. Aesthet Plast Surg 26:375–382
19. Cheng NX, Xu SL, Deng H et al (2006) Migration of implants: a problem with injectable polyacrylamide gel in aesthetic plastic surgery. Aesthet Plast Surg 30:215–225
20. Cohen JL (2008) Understanding avoiding, and managing dermal filler complications. Dermatol Surg 34(Suppl 1):592–599
21. El-Shafey ES (2008) Complications from repeated injection or puncture of old polyacrylamide gel implant sites: case reports. Aesthet Plast Surg 32:162–165
22. Kazachkov EL, Fridman AB, Friss SA (1998) Granulomatous pleurisy after mammoplasty induced by polyacrylamide gel. Arkh Patol 60:58–61
23. Köhler L, Schwedler S, Worret W (1997) Embolia cutis medicamentosa. Int J Dermatol 36(3):197
24. Lemperle G, Romano JJ, Busso M (2003) Soft tissue augmentation with artecoll: 10-year history, indications, technique and complications. Dermatol Surg 29:573–587
25. Lemperle G, Rullan PP, Gauthier-Hazan N (2006) Avoiding and treating dermal filler complications. Plast Reconstr Surg 118(3 Suppl):92S–107S
26. Narins RS, Beer K (2006) Liquid injectable silicone: a review of its history, immunology, technical considerations, complications and potential. Plast Reconstr Surg 118(3 Suppl):77S–84S
27. Vargas AF, Amorim NG, Pitanguy I (2009) Complicações tardias dos preenchimentos permanentes. Rev Brás Cir Plast 24(1):71–81
28. Fadanelli RG, Terres M, Bins-Ely C, Correa R (2007) Reconstrução de nariz após necrose por injeção de polimetilmetacrilato na face—relato de dois casos. ACM Arq Catarin Med 36(Suppl 1):154–156
29. Murata C, Provenzano J, Pereira MG (2002) Cegueira unilateral: complicação secundária à injeção de polimetilmetacrilato em procedimento de cirurgia estética—relato de dois casos. Rev Bras Oftalmol 61(6):454–457
30. Coiffman F (2008) Alogenosis iatrogenética. Una nueva enfermedad. Cir Plást Iberolatinoam 34(1):1–10
31. Salles AG, Lotierzo PH, Gemperli R, Besteiro JM, Ishida LC, Gimenez RP et al (2008) Complications after polymethylmethacrylate injections: report of 32 cases. Plast Reconstr Surg 121(5):1811–1820
32. Wolfram D, Tzankov A, Piza-Katzer H (2006) Surgery for foreign body reactions due to injectable fillers. Dermatology 213(4):300–304
33. Amin SP, Marmur ES, Goldberg DJ (2004) Complications from injectable polyacrylamide gel: a new nonbiodegradable soft tissue filler. Dermatol Surg 30(12 pt 2):1507–1509
34. Lemperle G, Rullan PP, Hazan NG (2006) Avoiding and treating dermal filler complications. Plast Reconstr Surg 118:92S–107S
35. Carpaneda CA (1997) Inflammatory reaction and capsular contracture around smooth silicone implants. Aesthet Plast Surg 21:110–114