When Hyaluronic Acid Alters its Rheology: Clinical, Ultrasonographic and Pathological Correlation

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Abstract: Hyaluronic acid has demonstrated itself as a highly successful non-invasive medical procedure for mitigating facial aging changes. This success is primarily attributed to its biodegradable or temporary nature, the reproducibility of aesthetic results, and the potential for dissolution through hyaluronidase. Despite its virtues, changes in the rheology of the product can occur, leading to alterations in its structure, resulting in the formation of visible, palpable nodules that are challenging to degrade with hyaluronidase. We present a case series of 9 patients in whom high-resolution ultrasound detected changes in the normal echographic appearance of hyaluronic acid suggestive of pseudosolidification, including increased echogenicity, a hyperechoic band inside the periphery of the deposits, the absence of degradation changes, and persistent, well-defined oval morphology. All cases showed no inflammatory activity on Doppler. In one case, the deposit was surgically removed during blepharoplasty, and histopathological analysis provided useful information to understand the mechanisms behind such complications.

Keywords: Hyaluronic Acid, Filler Complications, Dermatological Ultrasound, Doppler, Foreign Body Granuloma.

INTRODUCTION

The use of soft tissue fillers is a steadily increasing non-invasive procedure aimed at recovering lost facial volume during aging, reducing wrinkles and fine lines, improving skin appearance, and recovering lost volume with tissue repositioning (1). It is also described in conditions such as scleroderma or diseases causing facial atrophy, such as Parry-Romberg syndrome or localized scleroderma (2). According to the International Society of Aesthetic Plastic Surgery (ISAPS), in 2022, hyaluronic acid (HA) application was the second most performed non-surgical aesthetic procedure globally, following botulinum toxin application (3).

The ideal filler material must meet multiple characteristics, including being cosmetically effective, non-allergenic or immunogenic, having reproducible results, being non-carcinogenic, non-teratogenic, non-migratory, and cost-effective. Unfortunately, a substance meeting all these criteria has not yet been developed, leading to potential complications (4). Despite being described as a degradable material, hyaluronic acid can undergo rheological changes resulting in non-degradation, requiring multiple hyaluronidase injections (5). These changes can be identified through the use of high-resolution ultrasound, revealing variations in its usual echographic appearance (6). Identifying these ultrasonographic changes allows for better clinical management of patients and improved resolution of such complications.

STUDY TYPE

We conducted a descriptive, retrospective study of a case series involving 9 patients with clinically visible, palpable nodules that appeared after hyaluronic acid application. All patients underwent high-resolution ultrasound with a 24 MHz linear Hockey stick transducer with Doppler analysis, following established study parameters (7,8). Ultrasound findings were described in a table developed for the study (Table 1). Patients were referred to their treating physician for management, and a hyaluronidase dissolution protocol was applied. In one patient scheduled for blepharoplasty, nodules were surgically removed, and histological analysis was performed.

FINDINGS

In a series comprising 9 cases, an in-depth study was conducted to analyze variations in hyaluronic acid rheology using ultrasound as an exploration tool. The study population, mostly composed of females (77.78%), underwent meticulous ultrasound evaluations focusing on identifying multiple dermal deposits. The average age of participants was 37 years.

Among the 9 cases analyzed, 6 exhibited echogenic deposits, while the remaining 3 presented hypoechoic deposits. Although most cases showed well-defined borders in ultrasound images, exceptions were recorded, including one case with poorly defined borders and another with partially defined borders. The characteristic morphology of deposits in all cases revealed an oval and pseudocystic configuration.

Concerning internal deposit characteristics, dense particulate echoes were observed in all cases, with an additional hyperechoic halo identified at the internal margin in two cases.

The anatomical distribution of deposits varied, with 55% of patients presenting them in the infraorbital regions, 18% in the lower lip, 9% in the upper lip, 9% in the mentolabial region, and 9% in the nasolabial region bilaterally.(Figure 1)

Table 1: Presents ultrasound findings for the cohort of nine patients exhibiting rheological changes in hyaluronic acid.

Gender	Age	Echogenicity	Borders	Shape	Quantity	Average Transverse Diameter (mm)	Internal Characteristics	Anatomical location	Doppler	Skin planes	Diagnosis
F	25	Echogenic	Well-defined	Oval, Pseudocystic	Multiple	5,5	Dense particulate echoes	Lower Lip	Without increased vascularity	Superficial and deep subcutaneous tissue	Pseudosolidification
F	32	Echogenic	Well-defined	Oval, Pseudocystic	Multiple	12,9	Dense particulate echoes	Infraorbital Mentolabial	Without increased vascularity	Involving subcutaneous tissue reaching the muscular plan	Pseudosolidification
F	35	Hypoechoic	Well-defined	Oval, Pseudocystic	Multiple	10,7	Dense particulate echoes	Infraorbital	Without increased vascularity	Superficial and deep subcutaneous tissue and orbicular plane	Pseudosolidification
M	52	Echogenic	Well-defined	Oval, Pseudocystic	Multiple	5,2	Dense particulate echoes	Infraorbital	Slight increase in vascularity	Superficial and deep subcutaneous tissue	Pseudosolidification
F	40	Echogenic	Well-defined	Oval, Pseudocystic	Multiple	4,2	Dense particulate echoes, Hyperechoic halo at the inner edge	Infraorbital	Without increased vascularity	Herniation of infraorbital fat	Pseudosolidification
F	42	Echogenic	Ill-defined	Oval, Pseudocystic	Multiple	4,5	Dense particulate echoes	Upper Lip	Without increased vascularity	Superficial and deep subcutaneous tissue	Pseudosolidification
F	28	Echogenic	Well-defined	Oval, Pseudocystic	Multiple	4,2	Dense particulate echoes	Lower Lip	Without increased vascularity	Submucosa	Pseudosolidification
F	38	Hypoechoic	Partially defined	Oval, Pseudocystic	Multiple	7,5	Dense particulate echoes	Infraorbital Nasogenian	Without increased vascularity	Supraperiostial	Happy Bump
M	43	Hypoechoic	Well-defined	Oval, Pseudocystic	Multiple	6,5	Dense particulate echoes, Hyperechoic halo at the inner edge	Infraorbital	Without increased vascularity	Superficial and deep subcutaneous tissue and Supraperiosteal	Pseudosolidification

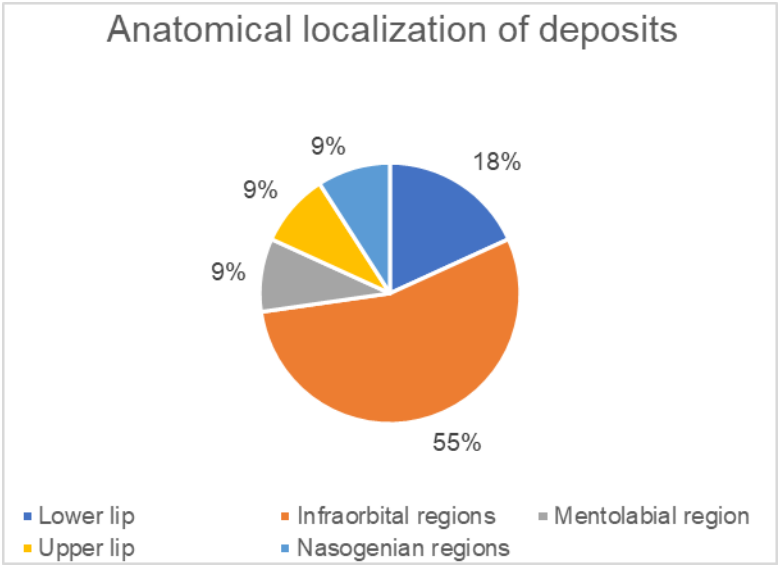

Figure 1: Anatomical Localizations of Deposits in a Cohort of Nine Patients with Rheological Changes of Hyaluronic Acid.

Doppler ultrasound evaluation revealed the absence of increased vascularity in 8 of the 9 cases, with a slight increase observed at the periphery of one deposit.

Regarding hyaluronic acid deposit planes, a predominance in subcutaneous tissue, both superficial and deep, was observed. In one instance, the deposit extended to the muscular plane, and in two patients with lip deposits, submucosal involvement was identified. In one case, the orbicular plane was also affected, and two cases had supraperiosteal deposits. One last patient had herniation of the infraorbital fat.

Finally, 88.89% of cases received an ultrasound diagnosis of hyaluronic acid pseudosolidification, while the remaining case was characterized as representative of the condition known as "Happy Bump."

DISCUSSION

Hyaluronic acid (HA) is a biodegradable or temporary filler material naturally present in the skin, specifically in the extracellular matrix of animal and bacterial tissues. It possesses a significant water-binding capacity, allowing it to be rapidly eliminated from the injection site. This natural elimination process is enhanced by the presence of hyaluronidase and free radicals in the skin (9). HA is the most widely used filler globally and is considered the ideal filler material (1). Chemically, it is a glycosaminoglycan composed of D-N-acetylglucosamine and D-glucuronic acid disaccharides (400 Da), which link through 1,4 B glycosidic bonds to form polymer chains (25,000 Da). These chains then join to create larger networks (up to 10 MDa) (9). To modify the characteristics of HA during the manufacturing process, substances such as cross-linking agents, viscosity modifiers, extrusion, gel consistency and hardness, and concentration are added. These modifications aim to prolong the duration of HA in tissues (5,9,10). Cross-linking agents like butanediol diglycidyl ether (BDDE) and divinyl sulfone (DVS) organize HA polymers into a network-like structure, reducing degradation by enzymes and free radicals post-application (9). Residual cross-linking agents or incomplete reactions with HA chains during production may result in substance artifacts, altering the expected product elimination time and increasing immunogenicity. These alterations may be responsible for changes in the rheology of the product and the development of visible and palpable nodules, as well as the lack of product degradation (2,8,9).

High-resolution ultrasound has proven to be the ideal diagnostic modality for the identification and characterization of various filler materials (11–13). In high-resolution ultrasound, HA is classically described as echogenic, oval, or pseudocystic foci (14,15). With degradation changes, deposits become more elongated. There may be some degree of increased echogenicity in the tissues surrounding HA deposits, considered normal, with no increased vascularity within or around the deposit upon Doppler examination (Figure 2). In our patient series, ultrasound findings suggestive of pseudosolidification due to changes in product rheology were identified, including an oval shape, absence of degradation, dense particulate echoes inside deposits, and a hyperechoic band around the deposits (Figure 3). Only one case showed a slight increase in vascularity at the periphery of the deposit, while in all other cases, vascularity was normal on Doppler examination. These nodules have been termed "Happy Bumps," distinct from inflammatory nodules referred to as " Red Angry Bumps" (16). The term "Happy Bump" was initially described for four cases of HA complications, where changes in the rheology of the product were evident, with direct visualization of product solidification remaining in the syringes post-patient injection (5). In this study, the authors described ultrasound findings of solid and isoechoic nodules without inflammatory activity on Doppler examination.

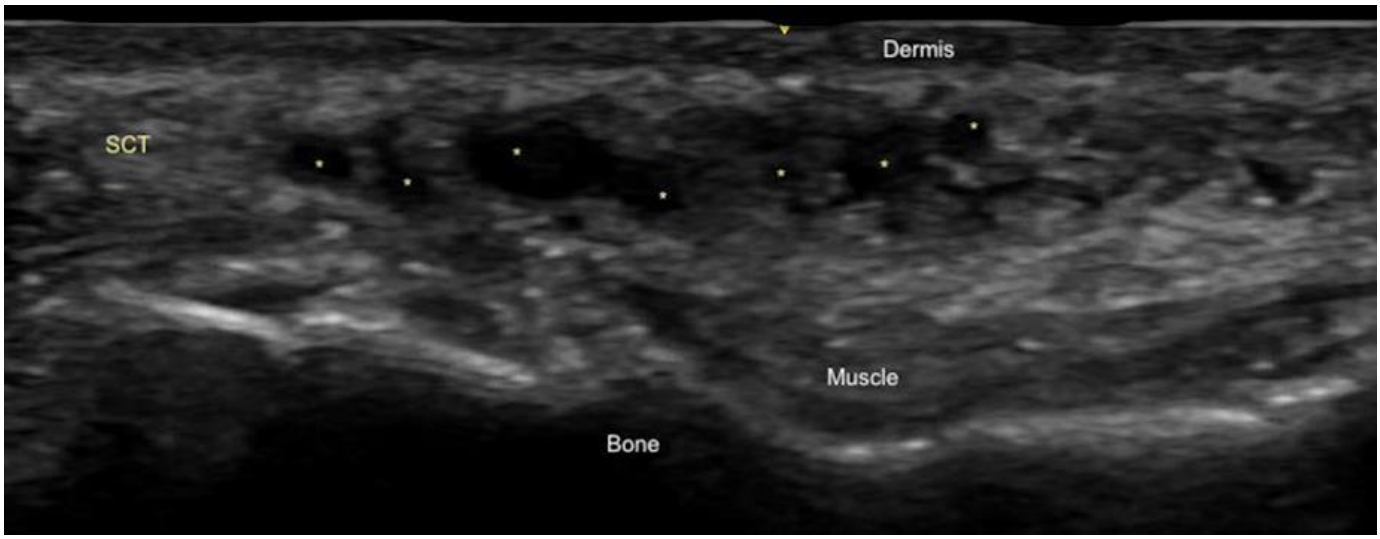

Figure 2: Longitudinal image of the nasolabial fold in grayscale. Yellow asterisks indicate the normal appearance of hyaluronic acid with multiple images: pseudocystic, oval, or round; anechoic. They are located in the subcutaneous cellular tissue (SCT).

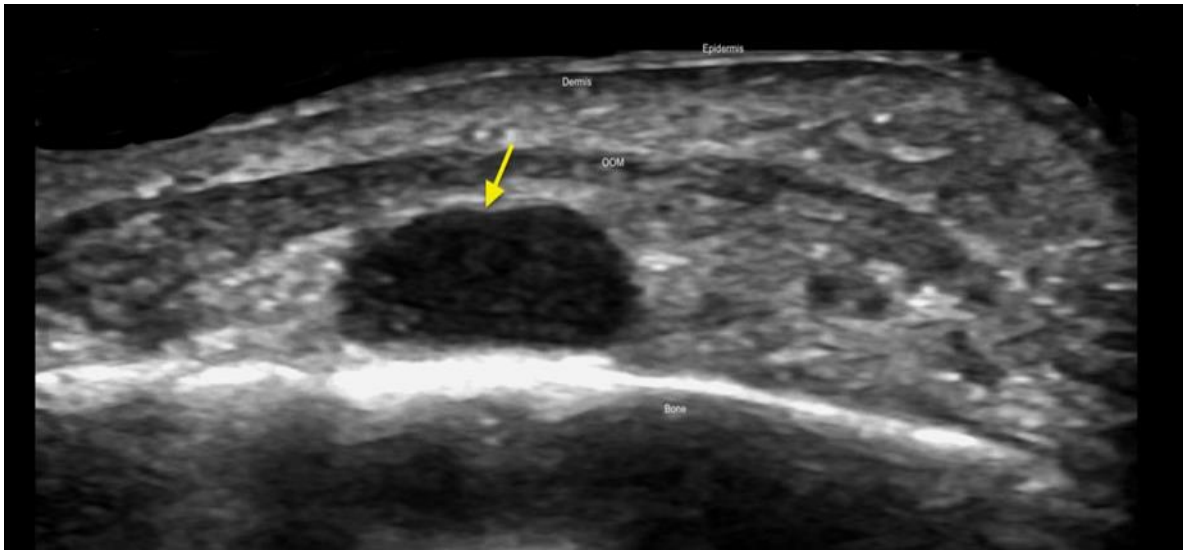

Figure 3A: Axial grayscale image. Shows a deposit of hyaluronic acid with pseudosolidification changes located in the zygomatic-malar region; it feels firm to the touch. The yellow arrow indicates an oval image with well-defined borders and dense echoes inside; it is located in the supraperiosteal region over the bony ridge. This deposit has been present for 17 months without signs of degradation. Orbicularis oculi muscle (OOM) is visible.

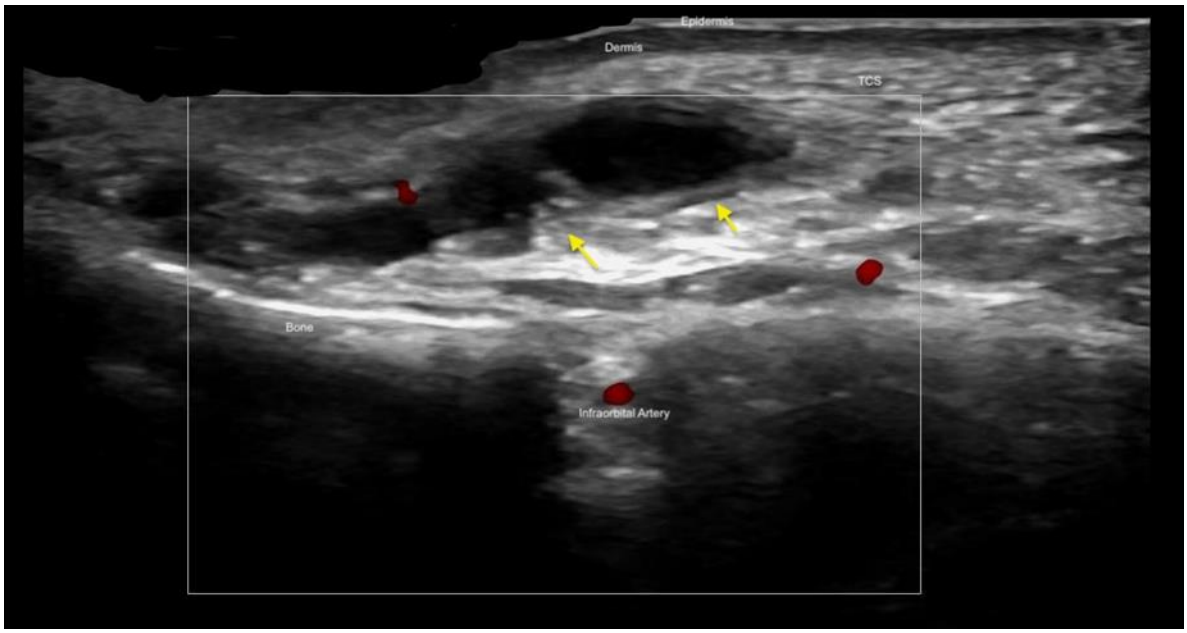

Figure 3B: Axial grayscale image. Displays a deposit of hyaluronic acid with pseudosolidification changes located in the infraorbital region; it feels firm to the touch. The arrow shows hyaluronic acid deposits with oval, confluent, pseudocystic images without degradation changes, with a hyperechoic band inside the periphery of the deposits, corresponding to pseudosolidification changes. Doppler examination shows no increased vascularity, distinguishing it from nodules termed 'Red Angry Bump.'

In an effort to better understand the pathophysiological mechanisms related to the development of this type of complication, some authors have conducted histopathological evaluations of the nodules, finding primarily thickening of the subcutaneous fibrous septa with a patchy perivascular lymphocytic inflammatory infiltrate in adipose lobules [6]. Meehan et al. reported a histopathological pattern specifically characterized by discrete granulomas closely packed with eosinophils (17). These two authors found an association between the development of these complications and histopathological changes specifically related to hyaluronic acids with Vycross technology. The appearance of such nodules has also been reported by other authors (18,19). In our study, one patient with the emergence of a solid and firm nodule in the infraorbital region refused to dissolve it with hyaluronidase and requested surgical removal due to the indication for blepharoplasty. During the surgical procedure, nodules were observed—oval, well-defined contours with a yellowish-white color and solid to the touch. They were extracted and sent for histological study (Figure 4). The histopathological examination revealed fibrinous material mixed with blood with a

markedly hyaline appearance. No epithelium or stroma was recognized for histopathological study (Figure 5). No inflamatory activity was found in the Hystopathology study, that confirms the abscent of inflammatory activity in Doppler exploration. In the case of our patient, while it is true that the fundamental histopathological finding is the presence of fibrinous material, different from what other authors have observed, it is striking that the product had the same Vycross technology.

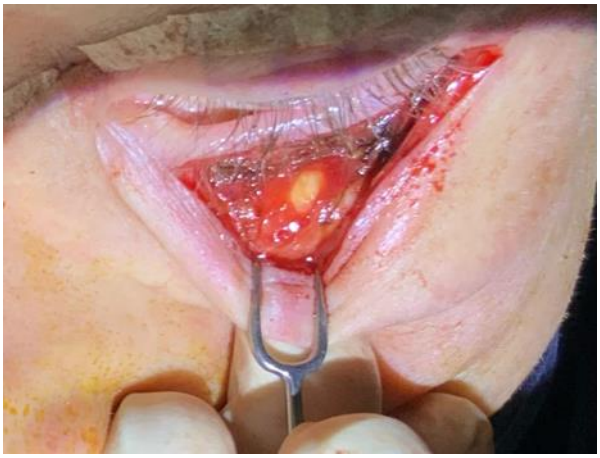

Figure 4A: Image of the surgical blepharoplasty procedure for the patient from Figure 2B. The hyaluronic acid deposit turned white- yellow.

Figure 4B: Image of the surgical blepharoplasty procedure for the patient from Figure 2B. The hyaluronic acid deposit turned white - yellow and, during extraction, was cream solid lumpy consistency.

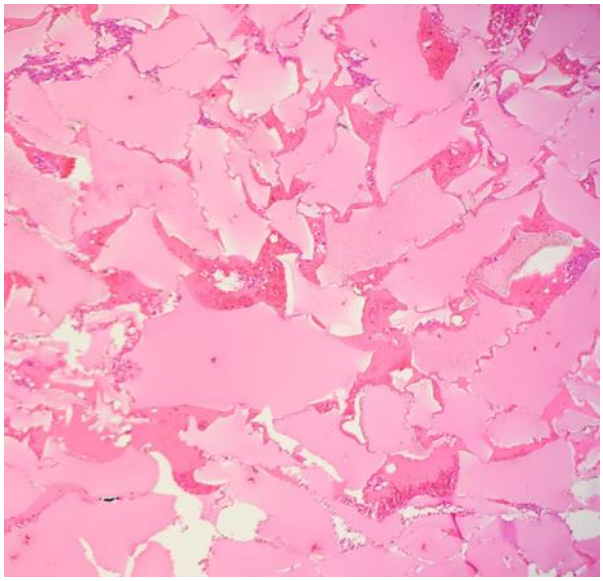

Figure 5: Biopsy of the nodule extracted during blepharoplasty shows fragments of hyaline and fibrinous material mixed with blood, with no evidence of epithelium or stroma for histopathological study.No inflamatory activity was found in the Hystopathology study, that confirms the abscent of inflammatory activity in Doppler exploration.

Complications secondary to the use of dermal fillers like hyaluronic acid can be immediate (within the first 24 hours), early-onset (24 hours to 4 weeks), or late-onset (more than 4 weeks). Additionally, they can be ischemic or non-ischemic (10,20). In the latter group, the most common complications include reactions at the injection site, pigment alterations, lumps or nodules, foreign body granulomatous reaction, ulcers, Tyndall effect, infection, and biofilm formation (10).

Lumps or nodules are a common complication that can occur days to weeks after HA application. They are not painful and are caused by inadequate application technique, superficial administration, excessive product, or poor selection of rheology according to the area being treated (21). Monitoring and observation of the nodule are recommended, but if it becomes persistent, it can be treated with needle aspiration, a small incision, or hyaluronidase (20).

On the other hand, nodules are an early or late complication that can be inflammatory or non-inflammatory. It has been described that their appearance may result from a type IV hypersensitivity response or an associated infection (5,10,20). It is believed that HA or bacterial products can act as possible allergens, facilitating an immune-mediated inflammatory reaction (5,6). Biofilm formation around HA and other dermal fillers has been documented using polymerase chain reaction techniques. Bacteria resistant to multiple antibiotics and difficult to culture, such as atypical mycobacteria, as well as commensal skin and oral cavity bacteria, have been found to become pathogenic in the presence of a foreign body (5,10,20,22). Treatment options include hyaluronidase, provided there is no active infection, as its application

could exacerbate the infectious process in the tissue (23). Other treatments described include infiltration with triamcinolone 0.1 mL and 5-fluorouracil 0.9 mL (40 mg/mL and 50 mg/mL presentations, respectively), given in two doses weekly, then two doses every two weeks, and finally two doses monthly until improvement. Alternatively, platelet-rich plasma application can be considered due to its antimicrobial effects (19). Regarding the use of antimicrobials, combined regimens with clarithromycin 500 mg and moxifloxacin 400 mg twice daily for 10 days, or ciprofloxacin 500-750 mg every 12 hours for 2 to 4 weeks, or minocycline 100 mg daily for up to 6 months are recommended (20,24).

CONCLUSION

Despite being considered the ideal filler material, hyaluronic acid is not exempt from developing various types of complications. This publication focuses on the use of dermatological ultrasound for the recognition of one such complication, which has been termed by some authors as a "happy bump," clinically corresponding to firm, solid nodules without inflammatory activity. In a group of nine patients with this symptomatology, we found a spectrum of characteristic ultrasonographic findings (Table 2). The recognition of these findings through dermatological ultrasound is crucial for the treatment and proper therapeutic approach for these patients.

Table 2: Spectrum of ultrasonographic findings suggestives of Pseudo-solidification of the Hyaluronic Acid

Spectrum of Ultrasonographic Findings Suggestives of Pseudo-Solidification of the Hyaluronic Acid
1.Increased echogenicity of the seudocyst deposit.
2.Hyperechoic band inside the wall of the deposit.
3.The absence of degradation changes.
4.Persistent, well-defined oval or roud morphology.

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