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Granulomas and nongranulomatous nodules after filler injection: Different complications require different treatments

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Summary Dermal fillers are widely used for facial rejuvenation and reconstruction and present fewer risks than surgical approaches. Nevertheless, several complications may occur, including nodule formation. A nodule is a clinical sign corresponding to different etiologies, such as overcorrection, infection, allergic reaction, or granuloma. However, their treatment represents a diagnostic challenge.

We present a retrospective review of 26 consecutive patients who underwent a biopsy for facial nodule formation more than 3 months after filler injections, to determine the diagnosis of the nodule and type of filler used. All patients were women (mean age, 57.8 years). Some patients suffered from different localizations: lip, 14 cases; nasolabial folds, 6; cheeks, 5; infraorbital region, 5; the glabella, 2; the temporal region, 1; and chin, 1 case. Only 5 (19.2%) patients knew the type of filler used, and in another 4 cases, the injector was able to provide some information. In 65.4% of cases, the filler type was unknown. Histopathological analysis revealed a "granulomatous" nodule in 30 sites and a "non-granulomatous" nodule in 4 cases. Concerning the type of filler, 5 different histopathological patterns were found.

Our results demonstrate that a clinical history and histopathological analysis whether to confirm or not to confirm the diagnosis of granuloma and to identify the type of filler are essential tools to achieve an accurate diagnosis of the problem-oriented treatment of nodules after dermal filler injections. We propose an algorithm for the management of nodules after filler injection.

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Introduction

There has been a significant increase of soft tissue filler procedures during the last few years and their use has trebled since 2000.[1] In the USA, they now represent more than 17% of the total of all cosmetic minimally invasive procedures (http://www.plasticsurgery.org/). Dermal fillers are used to restore facial volume or reduce wrinkles to create a younger and more attractive appearance.[2] Although these products are efficient and safe, they may trigger some complications. Unfortunately, complications can be encountered by using all these injectable products. Thus, it is important to discuss potential side effects with patients before the procedure, even if most are reversible and minor. Obviously, some complications are more prone to occur under specific conditions and depending on the products. Only a perfect knowledge of each filler and the anatomy will allow injectors to reduce the risk of complications or treat their eventual complications.[3]

Among all complications, "nodules" are not so rare. Even if the "nodule" is just a clinical description of a bulge at the injection site of a filler, in daily practice, many terms are used interchangeably to describe a "nodule," such as mass, lump, induration, abscess, or granuloma. Although all have distinct meanings, they are not easily distinguished from each other. However, it is fundamental to have a precise diagnosis as the treatment protocol is different for each one. Nodules can be classified according to the time of appearance following the injection: early (hours or days) and subacute or delayed (months or years later).[4] Early nonerythematous and nonpainful nodules appearing just after administering an injection is likely the result of an uneven distribution of a product that has been injected too superficially or in too large a quantity.[5] These nodules should be distinguished from inflammatory processes that may be due to an infection or immunological reaction.[6,7]

Any dermal filler has the potential to produce an inflammatory response as it will be recognized as a foreign body. The intensity and type of inflammatory or immunological reaction depend on the characteristics of each filler, e.g., particle size and biocompatibility.[8,9] These reactions can lead to subacute or delayed complications, such as granuloma.[10,4] We present here a problem-oriented approach from the diagnosis to the treatment of a "nodule," based on our extensive clinical experience in treating these complications after the filler injection. In particular, we highlight the pathologist's contribution that can guide the differential diagnosis and identify the filler type to improve the therapeutic decision.

Patients and methods

We conducted a review of the medical files of 26 consecutive patients at our institution, who underwent a biopsy for a facial nodule formation more than 3 months after filler injections. The indication for biopsy was to diagnose the type of nodule (granuloma vs. non-granuloma) and/or to clarify the type of filler if it was unknown. All patients were women (mean age, 57.8 years [42–81 years]) and all complained of a localized induration with or without pain at the site/s of the previous filler injection. Some patients suffered from different localizations: lip, in 14 cases; nasolabial folds, 6; cheeks, 5; infraorbital region, 5; the glabella, 2; the temporal region, 1; and in 1 case in the chin. All patients had been treated elsewhere, either in Switzerland or in other countries. Only 5 (19.2%) patients knew the type of filler that has been used, and in another 4 cases, the injector could provide some information. In 65.4% of cases, the filler type was unknown before the histopathological analysis. Before proposing a treatment, all patients underwent a punch or surgical biopsy to determine the diagnosis of the nodule and to identify the type of filler.

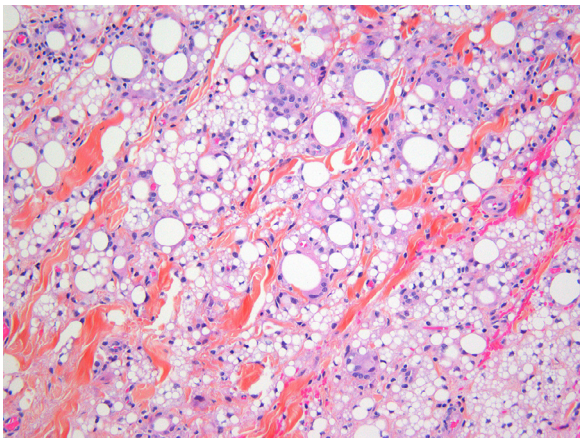


Figure 1 Granulomatous nodule containing silicone. Empty vacuoles of varied sizes surrounded by inflammatory cells and fibrotic tissue. (Hematoxylin-eosin staining 20x).

In 30 sites, the histopathological analysis revealed a "granulomatous" nodule and a "non-granulomatous" nodule in 4 cases. Concerning the type of filler, 5 different histopathological patterns were found: (Table 1)

1. empty vacuoles of varying size: this pattern could correspond to a silicone filler as during histologically processing the liquid silicone is dissolved and eliminated ($n = 19$) (Figure 1);
2. small translucent non-birefringent and pinkish polygonal particles with an irregular shape and size (45-60 μm), which are consistent with an acrylic product such as Dermalive® ($n = 4$) (Figure 2);
3. translucent non-birefringent and round microspheres of 30-40 μm: these particles matched with Artefill® and Artecoll®, composed of acrylic, which was received by one of these two patients ($n = 2$) (Figure 3);
4. small translucent but birefringent particles of different sizes and forms, some with spindle shape and others as microspheres of 30-40 μm ($n = 1$): this patient had received New-fill®, composed of polylactic acid and recently marketed as Sculptura®(Figure 4);
5. nonbirefringent, nontranslucent basophile flakes without any particles, compatible with hyaluronic acid ($n = 6$, 4 nongranulomatous cases and 2 granulomatous) (Figures 5 and 6).

Interestingly, all 4 "non-granulomatous" nodules contained only hyaluronic acid (example Figure 6). However, 2 sites showed a "granulomatous" nodule with hyaluronic

Table 1 Five different histological patterns of nodules.

	Translucent	Birefringent	Particles	Nodules
Silicone ($n=19$)	No	No	No	Granulomatous
Acrylic ($n=4$)	Yes	No	Different shape (45-60 μm)	Granulomatous
Acrylic ($n=2$)	Yes	No	Different shape (30-40 μm)	Granulomatous
Polylactic acid ($n=1$)	Yes	Yes	Different shape/size	Granulomatous
Hyaluronic acid ($n=6$)	No	No	No (flakes)	Nongranulomatous ($n=4$) Granulomatous ($n=2$)

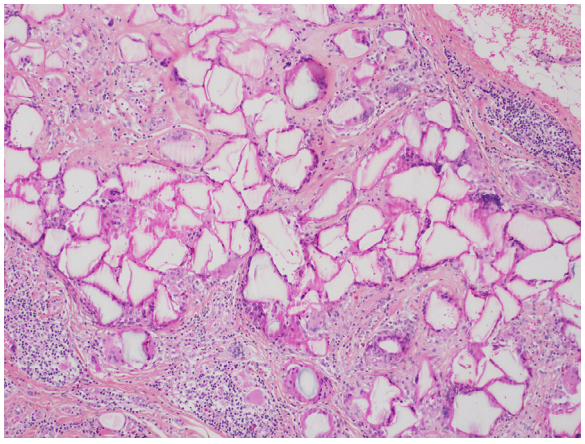


Figure 2 Granulomatous nodule containing acrylic particles (45-60 μm). Numerous pseudocystic spaces containing polygonal, pink, translucent foreign bodies with different sizes and shapes. They are not birefringent under polarized light microscopy (Hematoxylin-eosin staining 10x).

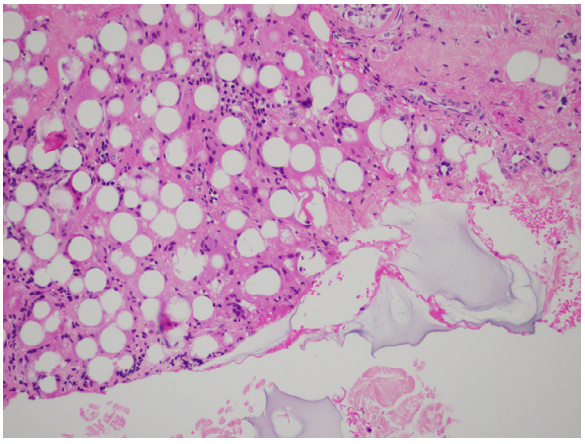


Figure 3 Granulomatous nodule containing acrylic particles (30-40 μm). Vacuoles of similar shape and size containing rounded sharply circumscribed, translucent, non-birefringent particles. Note at the bottom of the figure some basophilic flakes corresponding to hyaluronic acid without inflammatory reaction. The patient had two types of fillers injected at different times (Hematoxylin-eosin staining 20x).

acid (example Figure 5). Two patients had 3 different types of fillers at the same or adjacent sites.

Discussion

Complications can be encountered with all fillers, whether as a result of an improper injection technique or because of the nature of the product.[11] The rate is not high, but the significant increase in the use of these procedures has led to a corresponding increase of patients presenting complications.[1] There is a multitude of fillers, each with their own chemical constituents, indications, and effectiveness. Different factors must be considered, such as size, shape, and surface topography, with the chemical composition assuming an important role in the way in which the tissue reacts as well as the intensity and type of reaction. Fillers can be classified into three categories: resorbable (e.g., hyaluronic acid), biodegradable (e.g., polylactic acid), and permanent (e.g., silicone). The longer the product stays in the tissue, the higher is the risk to develop complications.[12] Permanent fillers (such as silicone) that persist indefinitely in the tissue, cause a high complication rate and long-term side effects. Therefore, these products should no longer be used although they have been used for many years in the past. Today, the products most used worldwide are resorbable or biodegradable polymers.

Any filler is considered first as a foreign material by the body, which attempts to eliminate it.[13,15,16]. Therefore, in response to the injection of any type of filler, the injection trauma per se and the product cause an acute inflammatory reaction characterized by swelling or erythema. Frequently, it lasts for one or two days and can be classified as an early injection-related event. Usually, the products, particularly resorbable fillers, are tolerated and resorbed without any complication over time (4-6 months). However, with some fillers, some patients develop a subacute immunological reaction or long-lasting inflammatory reaction that could result in foreign body granuloma.[14] This reaction evolves over time and is more prone to occur with biodegradable or permanent fillers.[9,17,18] Therefore, for the diagnosis and treatment of any nodules or inflammatory signs following filler injection, the distinction between immediate, delayed

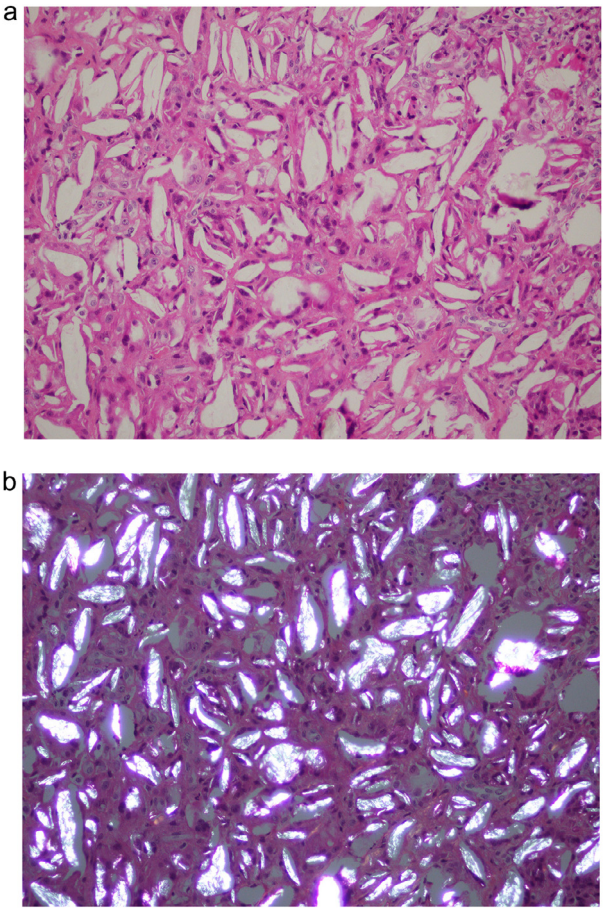


Figure 4 Granulomatous nodule containing polylactic acid. Multinucleated giant cells around fusiform or oval shape translucent particles (Hematoxylin-eosin staining x20) (Figure 4.1). Birefringent particles under polarized light examination (x20) (Figure 4.2).

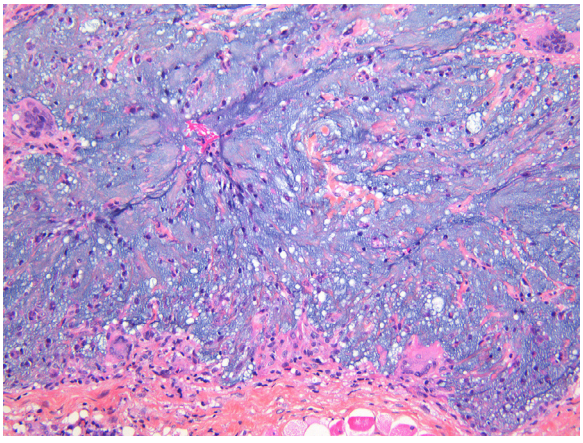


Figure 5 Granulomatous nodule containing hyaluronic acid. Non-birefringent non-translucent basophile flakes without containing any particles and surrounded by a large number of inflammatory cells (Hematoxylin-eosin staining 20x).

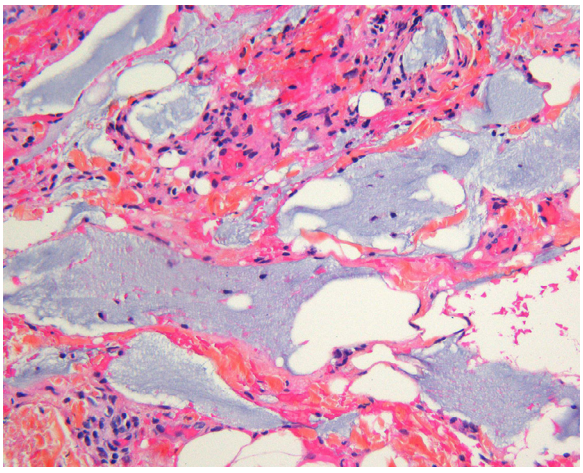


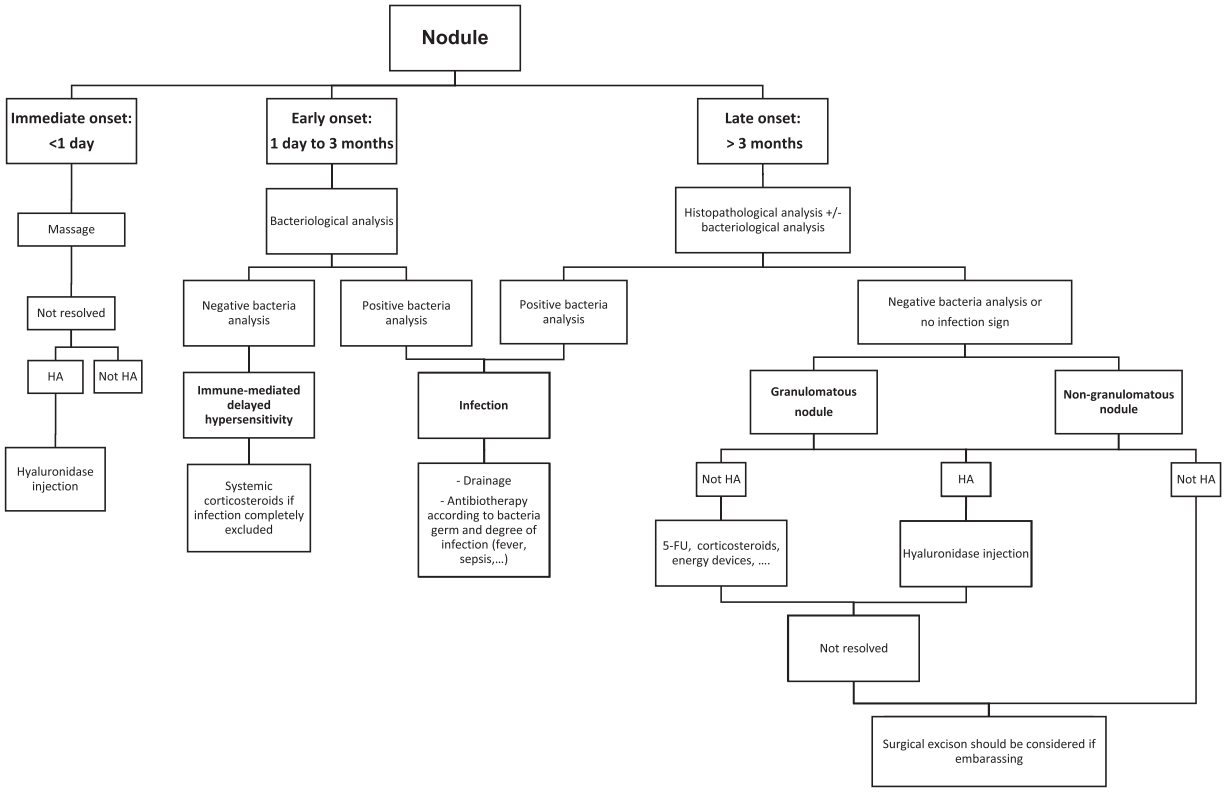
Figure 6 Granulomatous nodule containing hyaluronic acid. Non-birefringent non-translucent basophile flakes surrounded by rare inflammatory cells (Hematoxylin-eosin staining 20x).

hypersensitivity reactions, and late adverse reactions must be made, and the type of filler that has been used should be known.

A mass presenting at the time or within hours of injection is often due to product misplacement or edema.[20] Massage by mechanical displacement and diffusion will help to reduce and disperse the product.[4] If a hyaluronic acid product was used, the mass could be reduced by a hyaluronidase injection. When the nodules appear after a few hours or days, they should be considered as an infection or immunological reaction and treated accordingly.[21] In the case of suspicion of infection, a bacteriological sampling should be done before introducing any antibiotic treatment. The type and duration of antibiotic treatment vary according to the bacteriological analysis and degree of infection. If the bacteriological analysis is sterile, an immune-mediated delayed hypersensitivity reaction should be suspected, particularly if some specific products have been used. In that case, as suggested by Homsy et al., the treatment of choice is systemic corticosteroids, but only after excluding an infectious cause.[22] The role of histological assessment in immediate or early-onset complications is usually limited because of the lack of specific elements, whereas it becomes essential in delayed or late-onset complications.

Sometimes nodules appear 2–3 months or even years after the filler injection was administered. The most probable diagnosis of these late-onset nodules is granuloma. However, it may be also due to a hematogenous source of infection of the filler or reactivation of a biofilm, particularly if a permanent or biodegradable product has been used. The treatment of a granuloma, particularly when containing a nonresorbable filler, is complex and can be devastating. Therefore, before starting the treatment of any late-onset nodule, the diagnosis should be confirmed and the product known.

Granuloma is considered as a form of chronic inflammation that occurs in response to foreign material that cannot be phagocytosed by macrophages. Histopathological analysis typically shows a collection of foreign bodies, inside or



Graph Algorithm for the management of nodules after filler injection. HA: hyaluronic acid. Not-HA: fillers containing silicone fillers, acrylic, or polylactic acid particles.

outside inflammatory cells, surrounded and embedded in a connective and fibrotic tissue. The role of macrophages is to attempt to contain an external agent that is difficult to eliminate. The activation of T lymphocytes leads in turn to macrophage activation. Modified macrophages may develop an abundant cytoplasm resembling epithelial cells with indistinct borders called epithelioid cells. These seem to have a minor phagocytosis capacity as compared to macrophages, but a higher secretory purpose.[11] A collar of lymphocytes encircles the latter cells. Some macrophages may undergo fusion and then form multinucleated giant cells (Figures 1-5). By contrast, nongranulomatous nodules are an inert accumulation of a foreign body without an inflammatory reaction (Figure 6). Some may present some fibrotic tissues that could be induced by any filler, but their characteristics are different from a granuloma.

Different etiologies have been suspected to trigger granuloma formation, such as repeated injections, impurities within the filler, the volume injected, type and size of the particles, or even biofilm due to a systemic infection.[5] Lemperle et al. classified granulomas into three categories based on their clinical features, i.e., cystic granulomas, edematous granulomas, and sclerosing granulomas.[5] Even if the granuloma is clinically visible as a subcutaneous nodule, a histopathological analysis must be carried out as a nodule cannot be defined as granuloma unless a histopathological confirmation has been done. This will then allow to distinguish it from another diagnosis.[1,8,19]

Different treatment approaches have been proposed for the treatment of granuloma. Corticosteroids or 5FU (5-fluorouracil) injections are very useful in many cases by diminishing the inflammatory response.[7] However, the infection must be ruled out before starting corticosteroids and other immunosuppressant therapies. Indeed, a rebound effect must be feared at the end of their anti-inflammatory effect or they can cause the activation of the biofilm. If a hyaluronic acid product has been used, it can be reduced by the injection of hyaluronidase.[7] This enzyme hydrolyzes hyaluronan glycosaminoglycan polysaccharide complexes. Different protocols with variable doses (15 and 112.5 units) have been described to demonstrate its safety and efficiency.[23] However, practitioners must be aware that an allergic reaction can occur.[24] If granuloma containing hyaluronic acid persists after these conservative treatments, surgical excision should be considered.[25] Similarly, the surgical approach should be used if fillers other than hyaluronic acid have been used (e.g., silicone and polylactic) as there is no product to reduce them. These surgical procedures may be disastrous and leave important sequelae, but unfortunately, they are sometimes mandatory.

Therefore, the treatment of late-onset nodules strongly depends on the type of nodule and the product that has been injected. However, one of the biggest challenges for the treatment of nodules is the fact that the procedure is rarely done by the same injector, and as shown in our series, the product was unknown in more than 65% of cases. Thanks to histopathological analysis, we were able to adapt our treatment according to 5 different histopathological patterns that were identified and obtained a successful result. In the case of silicon-granuloma, recognized as giant cells containing empty vacuoles of varying size, we performed a surgical excision if the nodule was embarrassing ($n = 11$),

otherwise a conservative treatment was performed ($n = 8$). Similarly, surgical excision was performed for granuloma surrounding products of triangular particles of 45-60 μm (compatible with Dermalive®), microspheres of 30-40 μm (such as Artecoll®), and spindle-shaped microspheres of 30-40 μm (such as New-fill® or Sculptra®), only if nodules were very visible and embarrassing ($n = 5$). Otherwise, a conservative treatment with corticosteroids was attempted to reduce the nodule in 2 cases. In cases with hyaluronic acid, we were able to resolve completely the nongranulomatous nodule with hyaluronidase injection ($n = 4$). For granulomatous nodules containing hyaluronic acid ($n = 2$), as hyaluronidase injection was not sufficient, a surgical resection of remaining granuloma was performed.

The histopathological analysis is essential to confirm the diagnosis of granuloma and to identify the product used. It will also allow the surgeon to differentiate granuloma from a normal foreign body reaction and hence improve the treatment algorithm.

Conclusions

It has been said that the best way to manage complications is to avoid them. Knowledge of the properties of each filler, their indication and appropriate technique of injection as well as their potential adverse events is primordial. Given the massive popularity of such products, plastic surgeons and dermatologists will be increasingly confronted with associated complications, such as nodules. Treatment algorithms differ, depending on whether the nodule is inflammatory or not, its onset, and the filler used (Graph). Late adverse events are more prone to occur with permanent or semi-absorbable fillers. Unfortunately, in many cases, the patient does not remember which product has been injected or was never informed. In such circumstances, histopathological analysis resulting from a minimally invasive biopsy can become essential to orient the practitioner to choose the optimal treatment with the most suitable therapeutic arsenal and to avoid surgery whenever possible.

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