

Is it possible to avoid the late diagnosis of idiopathic granulomatous mastitis?

Abstract

Introduction: Idiopathic granulomatous mastitis (MGI) is a rare chronic inflammatory disease of unknown etiology. Its diagnosis is one of exclusion, it requires a histological sample that confirms the presence of granulomas, and specific cultures that rule out other causes of granulomatous disease. The initial mismanagement of these patients due to the lack of sampling for histological study and cultures, leads to a delay in diagnosis. There is no established treatment for this pathology, with surgical treatment and medical treatment with corticosteroids being the most used, either individually or in combination.

Objectives: To determine the incidence of MGI in those patients who consulted for inflammatory lesions of the breast and its incidence in those who finally underwent surgical treatment. Identify clinical characteristics that allow an initial diagnostic suspicion, and establish guidelines for surgical management that allow an early diagnosis.

Material and Methods: A retrospective, cross-sectional and descriptive work was carried out. The medical records of all patients undergoing surgical treatment of the breast for inflammatory lesions in the period from February 2018 to February 2020 were evaluated at the Gynecology and Obstetrics Service of the Sanatorio Güemes of Buenos Aires. Its clinicopathological characteristics, type of surgery performed and whether it required subsequent corticosteroid treatment were analyzed.

Results: In the period of time analyzed, 410 patients consulted for an inflammatory breast process, where only 10 of them (2.44%) had a diagnosis of MGI. If we consider those with surgical indication, the incidence of MGI amounts to 32.25% (31 patients). Ten patients had at least 2 previous consultations with a presumptive diagnosis of acute mastitis treated with different antibiotic regimens prior to the definitive diagnosis. Half of the patients required 2 surgical interventions prior to diagnosis. The average time interval elapsed between the first consultation and the definitive diagnosis was 4 months.

Conclusion: Patients with inflammatory breast disease with surgical indication, the differential diagnosis between abscessed acute mastitis and MGI should be considered, especially in the subpopulation of patients between 30-40 years of age, multiparous, and with multiple previous consultations for breast inflammatory processes refractory to antibiotic treatments. The surgical approach must include biopsy and specific cultures.

Keywords: granulomatous mastitis, breast abscess, mastitis

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Introduction

Idiopathic granulomatous mastitis (MGI) is a rare chronic inflammatory disease of unknown etiology. It was first described in 1972 by Kessler and Woodlock, but it was Cohen in 1977^{1,2} who described it in greater detail. From the histological point of view it is described as a granulomatous reaction of the breast with a variable association to autoimmune and hormonal disorders, infection and smoking. It is described in the literature in patients between 30 and 40 years old, who present a history of recent pregnancy and lactation.³ There are controversies regarding its pathogenesis. Apparently ductal ectasia caused by the accumulation of secretion rich in proteins in the ducts, would generate a chronic inflammation that would end up producing the rupture of the ducts and the direct contact of the secretion with the tissue stroma.^{3,4} This would produce a granulomatous type reaction where certain antibodies could be involved in the perpetuation of the pathology.⁴

It is usually of late diagnosis since its initial clinical manifestations are very similar to those observed in acute puerperal and non-puerperal mastitis, and can also resemble an inflammatory carcinoma,

with no pathognomonic clinical or imaging pattern.⁵ The most common ultrasound findings are the presence of a hypoechoic image communicated through a fistulous tract with the skin or with another hypoechoic area of variable size. It is also described as a heterogeneous area that generates parenchymal deformity.⁶ Like any inflammatory process, it is usually vascularized in its evaluation with Doppler. Mammographic findings are generally very nonspecific, diffuse asymmetries and thickening of the subcutaneous tissue are described, not being really useful for diagnostic orientation.⁷ They usually have a unilateral presentation.^{8,9}

Given its low prevalence, diagnostic suspicion usually appears after several episodes interpreted as acute recurrent mastitis refractory to different antibiotic treatments. To establish a diagnosis, it is necessary first to have a histological sample that confirms the presence of granulomas, and because its diagnosis is one of exclusion, we must secondly have specific cultures that rule out other causes of granulomatous disease.^{5,8} The initial mismanagement of these patients, due to the omission in taking samples for histological study and cultures, leads to a delay in diagnosis and therefore to the establishment of a medical treatment other than antibiotic therapy.

At the time of diagnosis, patients usually present large lesions, some abscessed or ulcerated.^{8,9} There is no established treatment for this pathology, with surgical treatment and medical treatment with corticosteroids being the most widely used, either individually or in combination.¹⁰ Surgical treatment has proven to be highly effective, reducing the cases of recurrence. In those cases where the disease is advanced the combination with corticosteroid treatment helps to control the inflammatory process.^{11,12}

Objectives

To determine the incidence of MGI in those patients with inflammatory lesions of the breast who consulted the Gynecology and Obstetrics Service of Sanatorio Güemes of Buenos Aires between February 2018 and February 2020. Evaluate the incidence of MGI exclusively in those who finally underwent surgical treatment. Identify clinical characteristics or risk factors that allow an initial diagnostic suspicion, and establish guidelines for the surgical management of patients with inflammatory breast disease with surgical indication that provide the necessary parameters for an early diagnosis.

Material and methods

A retrospective cross-sectional study was conducted on the computerized medical records of all female patients who consulted the Gynecology and Obstetrics Service of the Sanatorio Güemes of Buenos Aires with inflammatory breast lesions between February 2018 and February 2020.

Inclusion criteria

- Patients who consulted by guard or by outpatient clinics of the Sanatorio Güemes for inflammatory lesions of the breast.
- Patients whose histological diagnosis has been made in the Pathological Anatomy Service of the Sanatorio Güemes of Buenos Aires.
- Patients whose computerized medical records are available.

Exclusion criteria

Those patients for whom it is not possible to have access to paraffin plugs to confirm the histological diagnosis of granulomatous disease.

Age, history of parity, breastfeeding and smoking, clinical and surgical breast history, reason for consultation, clinical manifestations, imaging of the lesion and treatments received were analyzed.

Pathological reports of those patients who had undergone surgical treatment were analyzed. We evaluate type of surgery performed, pathological report and infectious study that consisted of a bacteriological study with Gram stain, Ziehl Nielsen stain, culture for Koch bacillus, mycological culture and common germs analyzed. The incidence of MGI was determined.

Finally we analyzed how many patients with MGI diagnosis required treatment with corticosteroids after surgery. All our patients were followed up to assess response to treatment and relapse rates according to the therapy used. The presence of complications related to the treatment carried out was analyzed.

Continuous variables are expressed as mean and standard deviation or median and interquartile ranges according to the considerations made according to their distribution. The categorical variables were expressed in absolute numbers and proportion.

Results

We identified a total of 410 female patients with a diagnosis of an inflammatory process of the breast evaluated between February 2018 and February 2020, through the computerized medical history of the Sanatorio Güemes.

Only 7.5% of them (31 patients) had a surgical indication. In all the surgeries, 2 samples of the lesion were taken, one for culture and the other for histopathological study.

Based on these results, we identified 10 patients with a diagnosis of MGI, which represent 2.44% of the total of patients with a diagnosis of mastitis and 32.25% of those with a surgical indication (Figure 1) (Figure 2).

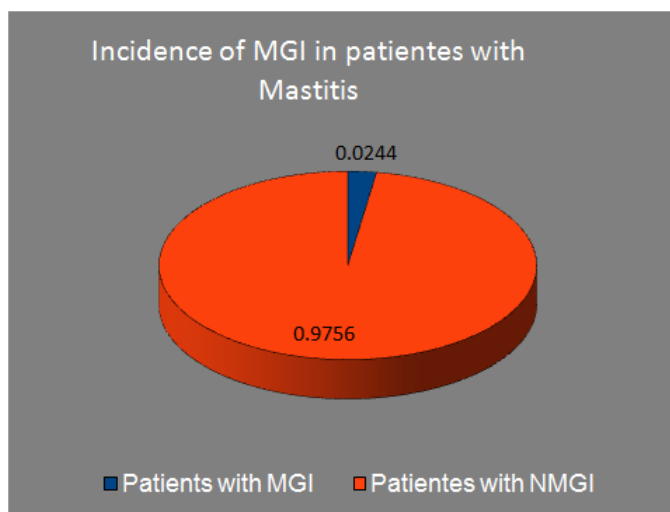


Figure 1 Diagnosis of MGI, which represent 2.44% of the total of patients with a diagnosis of mastitis.

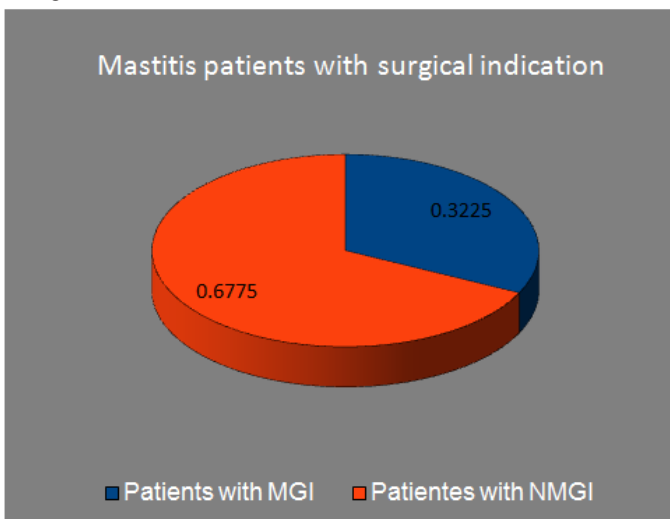


Figure 2 Diagnosis of MGI, which represent 32.25% of the total of patients with a surgical indication.

The mean age of the patients with a diagnosis of MGI was 36.4 years (SD±4.3 years, age range: 30-46years) while the average age of the patients without MGI (NMGI) was 39 years (SD±16.1; age range: 23-69years). Of the 31 patients evaluated, four had type II diabetes

mellitus, three were hypothyroid, two had hypertension, one psoriasis and the other asthma. The distribution of these pathologies in the 2 groups was even without statistical significance.

Regarding smoking habit, 70% of the patients with MGI were smokers, while only 24% of the patients in the NMGI group were smokers (Figure 3). In relation to obstetric history, 90% of the MGI were multiparous with average lactation periods greater than one year in each pregnancy and one of them was breastfeeding at the time of diagnosis. In the NMGI group, only 75% were multiparous with an average lactation period of 7 months, and 4 were actively breastfeeding (Figure 4).

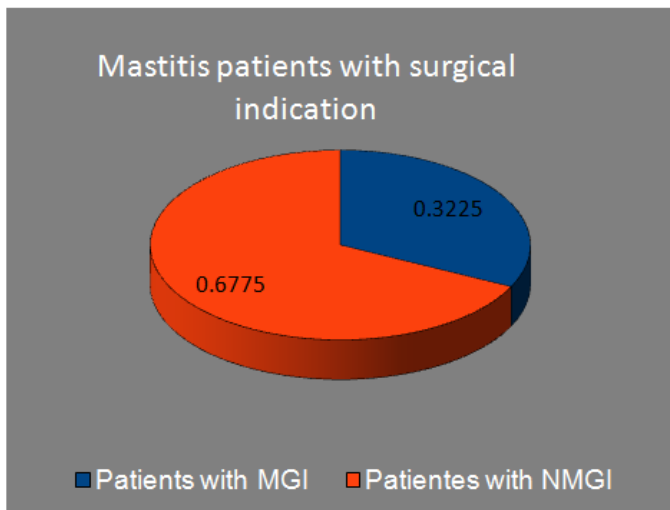


Figure 3 The patients in the NMGI group were smokers.

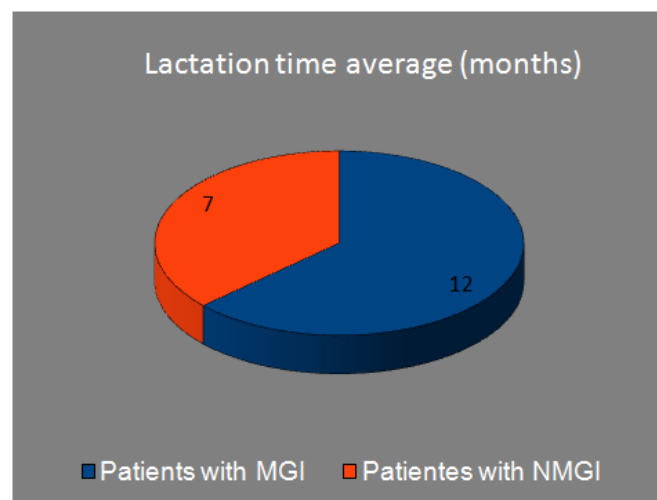


Figure 4 Average lactation period of 7 months.

All patients consulted due to nonspecific symptoms of an inflammatory process of the breast, that is, breast pain, erythema, a painful mass, and an increase in local temperature. Two of the patients with MGI and one of the NMGI group also had an ulcerated lesion (Image 1) (Image 2).

There were no significant differences regarding the laterality of the lesion in both groups. All patients underwent breast ultrasound and only one of them also had an MRI in a consultation outside the

institution. All lesions were described as heterogeneous and particulate collections or as heterogeneous nodules, with an average size of 3cm (Image 3) (Image 4).

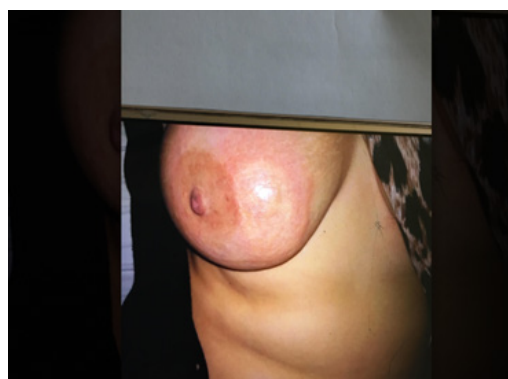


Image 1 The patients with MGI.



Image 2 The patients with NMGI.

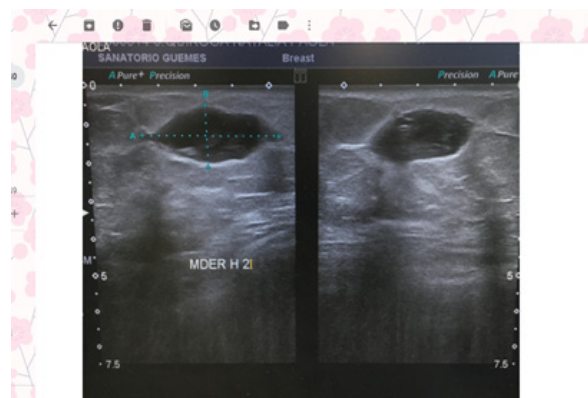


Image 3 Breast ultrasound and only one of them also had an MRI in a consultation outside the institution.

All the patients in the subgroup who underwent surgery had had a partial response to antibiotic treatment, and received between 2 and 3 different antibiotic regimens. The most widely used empirical regimens were Trimetropin Sulfamethoxazole (TMS) followed by Cephalexin (Table 1). Two of the patients with MGI (20%) and 4 patients in the NMGI group (19%) had previously undergone surgical drainage of breast abscess.

Regarding surgical treatment, 70% of the patients with MGI underwent breast abscess drainage (Image 5) and the other three had

a large duct resection (URBAN II). All NMGI patients underwent a collection drainage, except for one of them who underwent mastectomy + lymphadenectomy, this patient had an infected ulcerated lesion of the breast and during surgery had an intraoperative diagnosis of carcinoma invasive (Table 2).

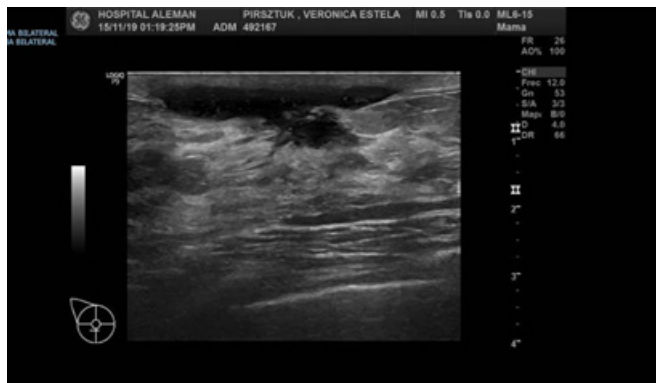


Image 4 Heterogeneous and particulate collections or as heterogeneous nodules, with an average size of 3 cm.



Image 5 The patients with MGI underwent a breast abscess drainage.

Table 1 (TMS:Trimethoprim sulfamethoxazole,AMC:Amoxicillin clavulanic)

First antibiotic scheme			
Patients with MGI		Patients with NMGI	
TMS	80% (8/10)	TMS	71,4% (15/21)
Cephalexin	20% (2/10)	Cephalexin	19% (4/21)
		AMC	9,6% (2/21)
Im second antibiotic scheme			
Patients with MGI		Patients with NMGI	
Cephalexin	20% (2/10)	Cephalexin	28,6% (6/21)
AMC	20% (2/10)	AMC	19% (4/11)
Ciproflacin	10% (1/10)	TMS	9,6% (2/21)
TMS	10% (1/10)	Clindamycin	4,8% (1/21)
Clindamycin	10% (1/10)	No second scheme	38% (8/21)
No second scheme	30% (3/10)		

Table 2 Patient had an infected ulcerated lesion of the breast and during surgery had an intraoperative diagnosis of carcinoma invasive.

Type of surgery in patients with MGT	
Abscess drainage	70% (7/10)
URBAN II	30% (3/10)
Type of surgery in patients with NMGI	
Abscess drainage	95% (20/21)
Mastectomy	5% (1/21)

Table 3 The results of the MGI cultures

Culture results			
Patients with MGI		Patients with WAG!	
Microorganism	'Number of patients	Microorganism	'Number of patients
Negative	90% (9/10)	Streptococcus Ep.	48% (10/21)
Polymicrobial	10% (1/10)	Staphilococcus A.	24% (5/21)
		Proteus M.	4% (1/21)
		Negative	24% (5/21)

In the NMGI group, the pathological anatomy reported acute and subacute inflammation in 76% of cases, while non-granulomatous chronic inflammation was reported in the remaining 24%.

The results of the MGI cultures were reported as negative in 90% of the cases (9 patients). In the remaining patient, the positive culture was reported as polymicrobial. No positive Koch or mycological cultures were detected. In the subgroup of non-MGI patients, 24% of the patients (5 patients) did not develop germs in the culture, the remaining ones developed positive cultures for Staphilococcus Epidermidis (10 patients), Staphilococcus Aureus (5 patients) and Proteus Mirabilis (1 patients) (Table 3).

In the case of patients with MGI, the time elapsed between the first consultation and the moment of definitive diagnosis was 4 months on average, while those without MGI had an average time from the first consultation to the diagnosis of 1 month.

Most patients with MGI (80%) required subsequent treatment with corticosteroids. The scheme used was Meprednisone, with an initial dose of 40mg /day for 2 weeks, followed by daily doses of 20mg, 10mg, 8mg, 4mg, 2mg and finally 1mg, for 2 weeks each dose. Just one patient did not require treatment with corticosteroids as she presented a good evolution after the surgical procedure. The remaining patient did not return to the consultation after surgical discharge, which is why corticosteroid treatment was not indicated. All of them were followed up for an average of 120 days (with a range of 21 to 425 days). Patients who received treatment with corticosteroids were jointly evaluated by the endocrinology service during treatment. None of them presented complications associated with it (Image 6). There were three patients with MGI who presented surgical complications, one presented a wound dehiscence with skin retraction that required a new surgery in the distant postoperative period for breast plastic, another evolved with an over infection of the surgical wound that required toilette and antibiotic treatment intravenous, and the third

a slight retraction of the skin. Two of the 7 patients who required corticosteroid treatment relapsed 30 and 150 days after the end of the corticosteroid treatment. Corticosteroid treatment was reinitiated and

both had a complete clinical response. All are currently free of signs of the disease.



Imagen 6 The endocrinology service during treatment.

Discussion

MGI is a rare chronic inflammatory disease of the breast that can clinically simulate lesions of an inflammatory carcinoma of the breast or acute mastitis, as described in the bibliography.^{5,9} According to our casuistry, the incidence of MGI in patients with inflammatory processes of the breast is extremely low (2.44%), while its incidence becomes more important (32.25%) when considering patients with surgical indication. We consider that it is in this last subgroup where the gynecologist should include MGI as one of the possible differential diagnoses.

The mean age of the patients with MGI was 36.4 years, similar to that described in the literature.^{5,12} We consider it important to highlight that, with a small sample size, the age standard deviation is limited. When evaluating the NMGI group, we found a mean age higher than what we expected.^{5,12} This can be explained by the small number of patients and the diagnostic variability. The 69-year-old patient from the NMGI group was the one who finally had a diagnosis of ulcerated invasive carcinoma, while the 54-year-old patient, also from the NMGI group, had a history of DBT II and developed acute abscess mastitis. The age range of MGI patients is much closer to the third decade of life, while the variability of NMGI patients is consistent with the feasibility of any infectious process.

Smoking is described in numerous works as a risk factor for developing MGI. In our population, the incidence of smoking is significantly higher in the MGI group than the NMGI (70% vs 24%).^{5,8}

Breastfeeding is also considered one of the risk factors for the development of MGI, being relevant the time of exposure to breastfeeding and the time between the last lactation period and the development of MGI.⁹ In our group of patients who underwent surgery, MGIs had a longer lactation period than NMGI patients (12 months vs. 7 months). In turn, only one of the MGI patients and four of the NMGI patients were in an active lactation period.

As mentioned above, MGI patients consult for signs and symptoms similar to those of other inflammatory pathologies of the breast, such as pain, erythema, lump and increased local temperature. No clinical differences were found between the MGI patients and the rest of

the evaluated patients, coinciding with what was analyzed in the bibliography.^{5,13} Regarding the imaging representation of the MGI, it does not present a specific pattern for its diagnostic orientation and ultrasound is usually represented as a collection or heterogeneous nodule of variable size.^{6,7,13} In our patients, no specific imaging pattern was found that would allow an early diagnostic suspicion.

Regarding surgical treatment, the most frequently performed surgery in patients with MGI was drainage of the collection. In agreement with what has been described by numerous authors, the surgical approach fulfills a therapeutic role and another diagnosis. Since it is a pathology whose diagnosis is one of exclusion, the surgical approach and the adequate sampling for biopsy and culture are essential to confirm the diagnosis. The anatomopathological reports of the biopsies obtained from the surgeries that allowed the diagnosis of MGI, described the lesion as a chronic inflammatory process with the presence of non-caseous granulomas with lymphocyte predominance and low in polymorphonuclear cells, which coincides with the descriptions made in the consulted bibliography.^{4,14} For the diagnosis of MGI, the cultures obtained during the surgical procedure or by percutaneous procedure must be negative. The results of the cultures of our patients with MGI were reported as negative in 90% of the cases (9 patients). In the remaining patient, the positive culture was reported as polymicrobial and was interpreted as contaminated.¹⁰

The late diagnosis of MGI is mainly due to the fact that its suspected diagnosis occurs after several episodes of recurrence treated with one or more antibiotic regimens before diagnosis.¹⁵ This was reflected in our patients with MGI, who had at least 2 episodes of recurrence with the consequent administration of 2 or 3 different antibiotic regimens. While those NMGI only 62% required a second scheme. For this reason, the average time elapsed between the first consultation and the definitive diagnosis of MGI was 4 months and that of NMGI was 1 month.

The most frequently described medical treatment for the control of MGI is corticosteroids, preferably Meprednisone. This can be administered as the only therapeutic or after a surgical procedure.^{10,13} In the case of our patients with MGI, 80% required corticosteroid treatment after surgery. Only one did not require corticosteroid

treatment due to a good postoperative evolution. Numerous complications associated with corticosteroid treatment have been described, including infections, hyperglycemia, and osteoporosis.⁷ However, we have not detected any complications associated with the treatment in our population. Unlike medical treatment, if we find mild complications in relation to surgical treatment. The combination of surgical treatment and medical treatment with corticosteroids was highly efficient for adequate remission and subsequent control of the disease.

Conclusion

According to the updated bibliography, MGI is a low-incidence entity. In the period of time analyzed, 410 patients consulted for an inflammatory process of the breast, where only 10 of them (2.44%) had a diagnosis of granulomatous mastitis. If we consider those with surgical indication, 31 patients, the incidence of MGI rises to 32.25%. It is precisely in this group of patients where we think that the differential diagnosis between acute abscessed mastitis and granulomatous mastitis should be considered, especially in those patients between 30-40 years of age, multiparous, and with multiple previous consultations for inflammatory breast inflammatory processes refractory to treatment. The importance of understanding this pathology lies in the fact that for its diagnosis an adequate surgical approach is necessary with taking a specific biopsy and culture. This would make it possible to improve the quality of care for these patients, avoiding late diagnoses and the need for second interventions to obtain samples.

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None.

Conflicts of interest

None of the authors has reported any conflicts of interest.

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