

Pigmented lesions of the oral mucosa: epidemiological survey of 172 cases with focus on differential diagnosis

Lesões pigmentadas da mucosa oral: estudo epidemiológico de 172 casos com foco no diagnóstico diferencial

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Abstract

The research purpose to perform a retrospective study of pigmented lesions in the oral mucosa and to discuss important aspects of their differential diagnosis and management in dental practice. **Methods:** This is a descriptive retrospective study of pigmented lesions in the oral cavity that were recorded and diagnosed at a referral service over a period of 28 years. **Results:** There were 172 cases of pigmented lesions among a total of 13,743 records, corresponding to a prevalence of 1.25% at this service. Females accounted for 61.6% of cases. The most affected age range was 31-40 years (23.8%). The most common anatomical location involved was the cheek mucosa (20.19%), followed by the lower lip (19.2%) and alveolar ridge (15.2%). Amalgam tattoo and melanotic macule (33.1%) were the most common pigmented lesions, followed by melanocytic nevus (21.6%). The lack of some information on the biopsy request forms was the main limitation of the study. **Conclusion:** Oral pigmented lesions were uncommon at the service analyzed, probably because not all of them were sent for histopathological analysis. However, a correct diagnosis is important so that patients receive adequate treatment.

Keywords: Oral mucosa; Melanocytes; Epidemiology; Diagnosis.

Resumo

O objetivo da pesquisa é realizar um estudo retrospectivo de lesões pigmentadas na mucosa bucal e discutir aspectos importantes de seu diagnóstico e tratamento diferenciado na prática odontológica. **Métodos:** Trata-se de um estudo retrospectivo descritivo de lesões pigmentadas na cavidade oral que foram registradas e diagnosticadas na clínica de Estomatologia e laboratório de Patologia Oral por um período de 28 anos. **Resultados:** Ocorreram 172 casos de lesões pigmentadas em um total de 13.743 registros, correspondendo a uma prevalência de 1,25% neste serviço. O sexo feminino foi responsável por 61,6% dos casos. A faixa etária mais afetada foi de 31 a 40 anos (23,8%). A localização anatômica mais comum envolvida foi a mucosa da bochecha (20,19%), seguida pelo lábio inferior (19,2%) e crista alveolar (15,2%). Tatuagem de amálgama e mácula melanótica (33,1%) foram as lesões pigmentadas mais comuns, seguidas por nevo melanocítico (21,6%). A falta de algumas informações nos formulários de solicitação de biópsia foi a principal limitação do estudo. **Conclusão:** Lesões orais pigmentadas eram incomuns no serviço analisado, provavelmente porque nem todas foram encaminhadas para análise histopatológica. No entanto, um diagnóstico correto é importante para que os pacientes recebam tratamento adequado.

Palavras-chave: Mucosa Oral; Melanócitos; Epidemiologia; Diagnóstico.

Introduction

Pigmented lesions of the oral mucosa are a diverse group of lesions that can vary from physiological pigmentations such as the characteristic gingival pigmentation of people with black skin to severe pathological pigmentations such as oral melanoma (1-2). Such pigmentation is caused by the accumulation of endogenous pigments, such as the increased local deposition of melanin and/or increase in the number of melanocytes, as well as an increase in the production and release of other pigments such as hemoglobin, hemosiderin and carotene. Pigmentation of the oral mucosa by exogenous material can also occur, for example, the deposition of amalgam which gives origin to amalgam tattoos (3,4,5). These physiological or pathological conditions in tissues are called pigmented lesions and the most commonly affected anatomical sites are the palate and buccal gingiva (1-3).

A wide range of pigmented lesions exist. However, lesions of different origins and clinical behaviors exhibit similar clinical features that require a differential diagnosis. These lesions can arise as multifocal or diffuse pigmentation, including racial physiological pigmentation, heavy metal-induced pigmentation (lead, silver, bismuth), and drug-induced pigmentation (phenolphthalein, minocycline, tranquilizers, antimalarial drugs, estrogen, some drugs used in patients with AIDS, and chemotherapeutic agents). In addition, there are diffuse pigmentations associated with systemic diseases such as Addison's disease and Peutz-Jeghers syndrome and solitary focal alterations such as oral melanotic macule, amalgam tattoo, melanocytic nevus and melanoma (3,5-6).

As mentioned, the cited lesions have different origins but exhibit similar clinical features in many cases and the correct differential diagnosis is therefore necessary. The dentist plays a key role in this diagnosis and careful anamnesis is important, including a thorough evaluation of the patient's medical and dental history, as well as careful extra- and intraoral examination. In some cases, complementary tests are necessary such as laboratory and extra- and intraoral imaging examinations to confirm the clinical diagnosis or to determine whether the pigmented lesion is the manifestation of an undiagnosed systemic disease (6).

In view of these considerations, studies investigating the frequency and diagnosis of pigmented lesions that can affect the oral mucosa are important. Therefore, the aim of this study was to analyze the prevalence and diagnosis of various oral pigmented lesions seen at a referral service in northeastern Brazil over a period of 28 years. In addition, important aspects related to the differential diagnosis and management of patients with these lesions in dental practice are discussed.

Materials and methods

This retrospective study was approved by the Ethics Committee (Approval No. 1.326.691/2015). The sample was selected intentionally by convenience sampling from biopsy records and histopathological reports stored in the archives of the Laboratory of Oral Pathology from 1990 to 2018.

Data such as sex, age range, skin color, anatomical location of the lesion, and histopathological diagnosis were collected for characterization of the sample. The collected data were tabulated, exported, and analyzed with the IBM SPSS Statistics 20.0 freeware (IBM Corp., Armonk, NY, USA). Descriptive statistics with calculation of absolute and relative frequencies within each group of lesions was used.

Results

There were 172 cases of pigmented lesions among a total of 13,743 records (1.25%) during the study period. The prevalence of lesions was higher among females ($n = 106$; 61.6%); with a female-to-male ratio of 1.6:1 (Table 1); most cases ($n = 142$; 82.5%) occurred in white patients, 84 of them females. Patients in the age range of 31-40 years were the most affected ($n = 41$; 23.8%).

Table 1. Frequency of pigmented lesions ($n = 172$) according to histological type of the lesion and epidemiological characteristics such as skin color, age range, and sex of the patients

	Gender		Total
	Male	Female	
Lesion	n (%)	n (%)	n (%)
Amalgam tattoo	18 (10.5)	39 (22.6)	57 (33.1)
Melanotic macule	21 (12.2)	36 (20.9)	57 (33.1)
Melanocytic nevus	17 (9.9)	20 (11.7)	37 (21.6)
Unspecific exogenous pigmentation	4 (2.3)	8 (4.6)	12 (6.9)
Melanoma	6 (3.5)	-	6 (3.5)
Melanoacanthoma	-	3 (1.8)	3 (1.8)
Skin color*			
White	36 (20.9)	48 (27.9)	84 (48.8)
Brown	13 (7.6)	24 (13.9)	37 (21.5)
Black	8 (4.6)	13 (7.7)	21 (12.3)
Age range (years)**			
2 - 10	4 (2.3)	1 (0.6)	5 (2.9)
11 - 20	3 (1.8)	7 (4.0)	10 (5.8)

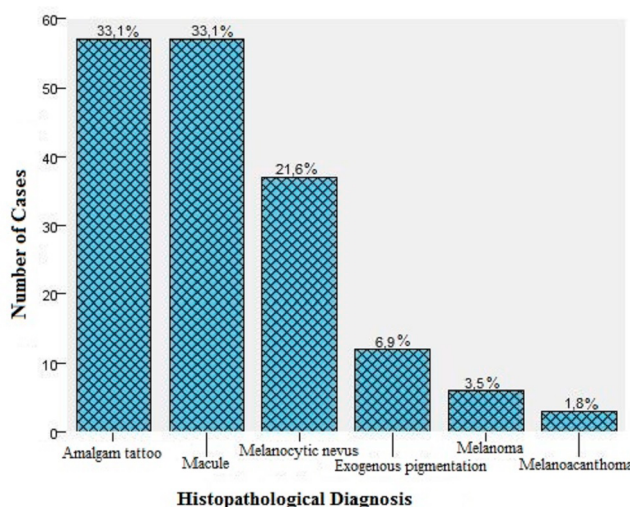
	Gender		Total
	Male	Female	
21 – 30	10 (5.8)	18 (10.5)	28 (16.3)
31 - 40	15 (8.7)	26 (15.1)	41 (23.8)
41-50	20 (11.7)	20 (11.7)	40 (23.4)
51 -60	9 (5.3)	12 (6.9)	21 (12.2)
61 - 70	1 (0.5)	11 (6.4)	12 (6.9)
71 - 80	2 (1.2)	3 (1.7)	5 (2.9)
81 - 90	2 (1.2)	-	2 (1.2)

Source: Laboratory of Oral Pathology, UFRN (Natal, RN).

*Skin color was not reported in the clinical records of 30 cases (17.4%). **The age range was not reported in the clinical records of 8 cases (4.6%).

Regarding the histopathological diagnosis, amalgam tattoo and melanotic macule were the most prevalent, with 57 cases each (Figure 1). Among the former, 39 cases were female and 18 cases were male, while 36 cases of melanotic macule were female and 21 cases were male.

Figure 1. Bar graph showing the distribution of pigmented lesions frequently found in the oral mucosa



The most commonly affected anatomical site was the cheek mucosa (n = 36), followed by the lower lip (n = 33) and alveolar ridge (n = 26). It should be noted that in some cases the same lesion occurred at more than one site, such as exogenous pigmentation in which the cheek mucosa and alveolar ridge were simultaneously involved in three cases due to graphite pencil chewing and the cheek mucosa and gingiva in one case (Figure 2A and 2B). Regarding melanoacanthoma, the cheek mucosa and lower lip were simultaneously involved in two cases (Figure 3A, 3B and 3C) and the hard and soft palate in one case (Table 2).

Figure 2. Clinical and radiographic features of amalgam tattoo. A: Blue spot in the lower alveolar ridge clinically compatible with amalgam tattoo. B: Radiopaque fragment suggestive of amalgam pigmentation

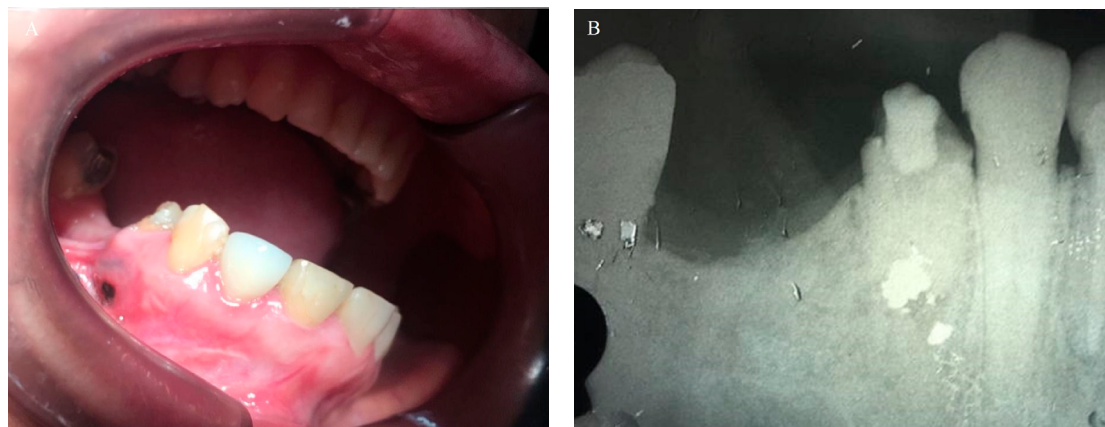


Figure 3. Clinical and histopathological features of oral melanoacanthoma. A: Multiple brown macular lesions in the cheek mucosa (bilateral) and posterior upper alveolar ridge. B and C: Morphological features of oral melanoacanthoma showing acanthotic epithelium (B) (10x magnification) with intense melanin pigmentation of basal layer cells (C) (40x magnification)

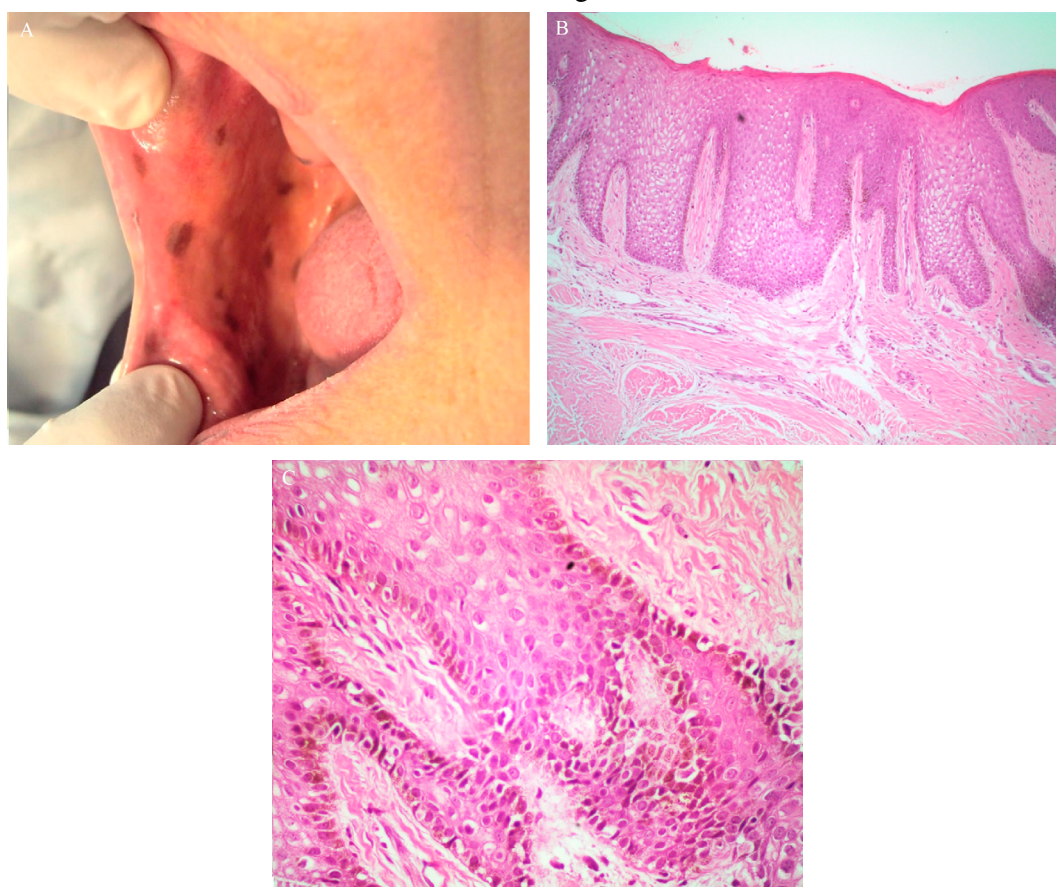


Table 2. Frequency of pigmented lesions (n = 172) according to anatomical location and histopathological diagnosis

Anatomical location	Lower lip	Upper lip	Hard palate	Soft palate	Gingiva	Retromolar region	Floor	Vestibule	Tuber maxillae	Tongue	Alveolar ridge	Cheek mucosa	
Histopathological diagnosis	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	Total
Amalgam tattoo	2	-	3	-	9	4	4	-	-	-	15	12	49*
Melanotic macule	20	2	4	1	10	1	-	-	2	-	8	9	57
Melanocytic nevus	6	3	5	2	2	2	1	1	-	2	1	10	35*
Unspecified exogenous pigmentation**	2	1	2	-	1	-	-	-	-	-	2	4	12
Melanoma	2	-	3	-	1	-	-	-	-	-	-	-	6
Melanoacanthoma**	1	-	1	-	-	-	-	-	-	-	-	1	3
Total	33 (19.2)	6 (3.5)	18 (10.4)	3 (1.8)	23 (13.3)	7 (4.0)	5 (2.9)	1 (0.6)	2 (1.2)	2 (1.2)	26 (15.2)	36 (20.9)	162 (94.2)

Source: Laboratory of Oral Pathology, UFRN (Natal, RN).

*The anatomical location was not reported in 10 cases, corresponding to 5.8% of the sample.

**In some cases, the same lesion involves more than one site in the oral cavity; thus the total frequency was 98.65%. In exogenous pigmentation, the cheek mucosa and alveolar ridge were affected in 3 cases and the gingiva and cheek mucosa in 1 case. In melanoacanthoma, the cheek mucosa and lower lip were involved in 2 cases and the hard and soft palate in 1 case.

Discussion

Studies of the prevalence of oral lesions are important to know the health conditions and treatment needs of a population. Comparison of the results of this survey with other studies on the prevalence of pigmented lesions was relatively difficult because of the small number of reports using the same approach to analyze the frequency of pigmented lesions as done in the present study. We therefore highlight the importance of this study since it allows to trace the epidemiological profile of these common lesions in the oral mucosa that are often difficult to diagnose, especially when associated with systemic conditions (3).

Oral pigmented lesions were uncommon at the service studied, accounting for only 1.1% of all 13,743 lesions recorded. This finding was probably due to the fact that several pigmented lesions are not sent for histopathological analysis because its clinical diagnosis is sufficient and no need to send it to histopathological analysis. For the correct diagnosis of this group of lesions, the dentist or stomatologist must have knowledge about their etiology, clinical features such as color, shape and size and diagnostic methods, must indicate a biopsy when necessary to rule out the possibility of malignancy, and must establish the adequate treatment and follow-up for the patient. In many cases, a biopsy is fundamental to establish the correct diagnosis and particularly to rule out melanoma (3,5-6).

The majority of oral pigmented lesions have melanin as the pigment of origin. Melanin is an endogenous pigment of variable color ranging from yellow to black, which is produced by melanocytes present in the basal layer of the oral epithelium (1). Alterations or disorders related to an increased deposition of melanin and other pigments can be triggered by trauma, infection, habits (smoking, chewing gum, foods), medication use (antimalarial agents, minocycline), and systemic factors such as Addison's disease, Peutz-Jeghers syndrome and tumors. Racial melanosis is a physiological condition of variable frequency in different ethnic groups and the gingiva is the most affected site in the oral cavity (1,7-8). In the present study, there were no biopsies of physiological pigmentation as diagnostic tests are not necessary in this case since this condition is associated with the natural deposition of melanin due to race and does not pose any risk to the patient. In this situation, some patients opt for esthetic correction such as high-power laser therapy.

Melanotic macule, melanoma, melanoacanthoma and melanocytic nevus are members of the group of solitary pigmented lesions (4). However, melanoacanthoma can exhibit a diffuse distribution in the oral cavity and can affect multiple sites (3-4,9). Despite their diffuse distribution, melanoacanthoma lesions often regress spontaneously and only continuous follow-up of the patient is necessary in these cases.

Melanotic macules are the most common melanocytic lesions in the oral cavity (5-8). Clinically, this condition is characterized by a flat brown lesion that can appear

on the lips, gingiva, buccal mucosa, and hard and soft palate (5,10). In agreement, our findings revealed melanotic macule as the most common lesion in the lower lip, followed by the cheek mucosa and alveolar ridge. All lesions were flat and had a brown color, as reported in the literature (3-5,10).

In the case of a histopathological diagnosis of melanotic macule, the clinician should investigate its association with systemic conditions. Particularly in the presence of multiple melanotic macules, an association with systemic alterations such as Laugier-Hunziker syndrome is possible, which is characterized by macular hyperpigmentation of the lips and oral mucosa, in addition to pigmented streaks on the nails (11).

Another systemic condition is Addison's disease, which in the oral cavity manifests as macules or diffuse brown plaques associated with generalized hyperpigmentation of the skin, especially in the regions of the elbows and knees (12). Another important systemic condition in which the patient exhibits multiple melanotic macules is Peutz-Jeghers syndrome whose main differential diagnosis is Laugier-Hunziker syndrome. Peutz-Jeghers syndrome is an autosomal dominant condition characterized by mucocutaneous pigmentation in the perianal region, genital mucosa and acral skin, gastrointestinal hamartomatous polyps, and a predisposition to cancer. In the oral cavity, hyperpigmented macules may be observed on the lips and oral mucosa (11).

Melanocytic nevus is a benign lesion that is rare in the oral mucosal and can be congenital or acquired. It is composed of nevus cells derived from the neural crest (7). Some authors suggest mutations in the BRAF gene in acquired lesions. Melanocytic nevus has three stages of clinicopathological development: the first stage of development consists of the presence of a well-delimited brown or black macule measuring less than 6 mm, in which nevus cells are organized into theca cells that are confined to the epithelium and connective tissue (junctional). With the proliferation of nevus cells, the lesion becomes raised, forming a papule in which the theca cells are found at the junction between the epithelium and connective tissue (compound). Over time, the nevus loses its pigmentation and the surface becomes papillomatous and theca cells are found only in connective tissue (intramucosal) (7-8).

Only few cases of melanocytic nevus have been reported in the literature; however, once identified, this lesion must be given due importance because of its clinical similarity with early-stage oral melanoma. This lesion can occur at any age and develop on skin of any color. A predilection for the third and fourth decades of life has been reported and approximately two-thirds of cases affect women with a mean age of about 35 years (7). These data agree with our results considering the anatomical location of melanocytic nevus, gender, and age estimate.

Oral melanoma is a rare malignancy arising from the neoplastic transformation of melanocytes or nevus cells. A marked feature of melanoma is its hyperpigmentation that can range from brown and black to blue and red, or even discoloration (13,14).

Melanomas exhibit an irregular margin and generally measure 6.0 mm in diameter. According to some authors, there is no sex predilection. However, reports in the literature show a higher prevalence of oral melanoma among Hispanics, Africans and Asians and between the fourth and seventh decade of life, as well as a male predilection (13), in agreement with our results showing a higher prevalence in males.

According to some authors, oral melanoma arises from apparently intact mucosa but might be preceded by a pre-existing dysplastic nevus. In most cases, the early lesions are black-bluish or dark brown and start as a focal macular lesion that progresses rapidly (1,3-4,13-14). In the oral cavity, melanoma mainly affects the palate and gingiva but can also involve the cheek mucosa and lips (13-14), in agreement with the cases diagnosed in the present study in which the most commonly affected sites were exactly the palate (hard), gingiva and lip (lower).

Melanoacanthoma is a rare benign lesion that generally occurs in dark-skinned women. Some clinical and histological features, such as rapid growth, history of trauma, possibility of lesion regression, presence of chronic inflammation and increased vascularization, support the hypothesis of a reactive process (7-8). This condition is generally characterized by flat or slightly raised black, solitary or diffuse lesions on the oral mucosa (3-4,9). These characteristics agree with the results of the present study in which melanoacanthoma affecting multiple sites was observed in three cases, including two cases involving the cheek mucosa and lower lip and one case involving the hard and soft palate. Female patients between the third and fourth decade of life were the most affected. The cheek mucosa was the most common site of melanoacanthoma, corroborating the findings of Lakshminarayanan et al. (15), Cantudo-Sanagustín et al. (6), and Tavares et al. (5).

Together with melanotic macule, amalgam tattoo is the most common pigmented lesion affecting the oral mucosa (5-6,15). Amalgam tattoo differs from melanocytic lesions by its exogenous origin. This lesion is caused by the introduction of silver particles from amalgam alloy in the oral mucosa during restorative procedures or removal of restorations. Amalgam tattoos frequently involve the gingiva and alveolar ridge near amalgam restorations (3-5). In the present study, amalgam tattoo (33.1%) and oral melanotic macule (33.1%) were the most common lesions. Amalgam tattoos more frequently occur in female patients, and the alveolar ridge, cheek mucosa, gingival and floor of the mouth are the most commonly affected sites. In some situations in which the patient does not know the origin of the lesion, identification of amalgam restorations near the lesion is not possible or silver fragments cannot be identified by radiographic examination, an excisional biopsy is necessary to rule out melanoma (3-4,9).

Other exogenous pigmentations can affect the oral mucosa to a lesser extent, especially heavy metal-induced pigmentation (5,13-14). Studies show that identification

of the pigment is generally difficult, as the patient is unable to report the origin of the lesion in most cases (3-5). Similarly, there were 12 cases (6.9%) in the present study in which the lesion was caused by a nonspecific external pigment. The present results highlight the important mission of the clinician and pathologist to establish the correct diagnosis of pigmented lesions that can affect the oral mucosa because of their often similar clinical features but different origins and clinical evolution.

Conclusion

The results of this study led us to conclude that oral pigmented lesions were uncommon at our service. Amalgam tattoo was the most prevalent entity, followed by oral melanotic macule. The correct diagnosis of pigmented lesions in the oral mucosa often represents a challenge for dentists because of the wide range of differential diagnoses. Thus, to establish the correct diagnosis, careful evaluation of disease history combined with detailed clinical examination, anatomopathological evaluation and, in some cases, complementary laboratory tests are necessary to rule out or confirm the association of these lesions with systemic conditions.

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