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Oral involvement in sarcoidosis: report of 12 cases

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Summary

Aim: To assess the clinical features, treatment and outcome of oral sarcoidosis and to determine whether oral involvement is associated with a particular clinical phenotype of sarcoidosis.
Design: Multicentric retrospective study.
Methods: Retrospective chart review. Each patient was matched with four controls.
Results: Twelve patients (9 women, 3 men) were identified. Their median age at sarcoidosis diagnosis was 38 years. Oral involvement was the first clinical evidence of sarcoidosis in seven cases and was a relapse symptom in five cases. Clinical presentations were nodules ($n=7$) or ulcers ($n=5$) and were mostly solitary. The tongue was the commonest site affected ($n=4$), followed by lips ($n=3$), oral mucosa ($n=2$), palate ($n=2$) and gingiva ($n=1$). Patients with oral sarcoidosis were significantly younger and had more frequent lacrimal or salivary glands and upper airway tract clinical involvement than the controls; increased angiotensin-converting enzyme was less frequent in oral sarcoidosis. Multiple treatments of oral sarcoidosis were used: no treatment ($n=3$), surgery ($n=2$), corticosteroids ($n=7$), hydroxychloroquine ($n=3$), methotrexate ($n=2$), doxycycline ($n=1$). Methotrexate was efficient in one patient, hydroxychloroquine showed benefit in only 1 out of 3 patients. Three patients presented oral relapses. After a mean follow-up of 6 years, 10 patients experienced a complete ($n=7$) or partial ($n=3$) remission of oral sarcoidosis; stability was observed in the remaining two cases.
Conclusion: Although oral manifestations of sarcoidosis are unusual, physicians should be aware that this specific localization is frequently the first manifestation of the disease. Treatment modalities range from observation in asymptomatic patients to immunosuppressants for severe involvement.

Introduction

Sarcoidosis is a chronic systemic disorder of unknown aetiology characterized, in affected organs, by an accumulation of epithelioid granulomas without caseation or staining for infectious agents and derangement of the tissue architecture.[1] Sarcoidosis affects multiple organs, especially the lungs, lymph nodes, skin and eyes. In the maxillofacial region the salivary glands are frequently involved and xerostomia or bilateral parotid swelling are sometimes present.[2,3] On the contrary, oral sarcoidosis, defined as lesions that occur in the soft tissues of the oral cavity, is considered to be rare with an unknown prevalence. A recent review of the English and French-language literature showed only 58 well-documented cases of sarcoidosis affecting oral soft tissues (jaw bones and salivary glands involvements being excluded).[4–17] Most cases exist as single or double case reports. Oral involvement usually concerns patients with chronic multisystemic sarcoidosis and appears as the first manifestation of the disease in one-third[5] to almost two-thirds[7] of patients. Clinically, most cases appear as non-tender swelling or nodular lesions, firm to the touch. Sarcoidosis localization of the mouth was described most often in the lips, hard and soft palate, buccal mucosa, gingivae, tongue and tonsils. Therapy of sarcoidosis-related oral involvement remains controversial. In the literature review, different treatments have been employed ranging from no specific therapy to surgical excision.[8,10,12,13] Systemic procedures include steroids, methotrexate, hydroxychloroquine and minocycline.

In light of these data, we conducted a multicenter retrospective study of 12 cases of oral sarcoidosis from the French sarcoidosis group (Groupe Sarcoïdose Francophone (GSF)). The aims of the study were: (i) to assess the clinical features, treatment and outcome of oral sarcoidosis; and (ii) to determine whether oral involvement is associated with a particular clinical phenotype of sarcoidosis in comparison with patients presenting extra-buccal manifestations of sarcoidosis.

Patients and method

Patients with oral sarcoidosis

Due to the retrospective nature of the study, it was exempted from the University of Lyon IRB (Institutional Review Board) approval. The authors have read the Helsinki Declaration and have followed the guidelines in this study. The design of this study was presented at the annual meeting of the GSF group in June 2010. Physicians belonging to the GSF were questioned by email about patients known to them with oral manifestations of sarcoidosis. Twelve patients from five different French centres (Croix-Rousse Hospital, Lyon; Lyon-Sud Hospital, Pierre-Benite; Montbeliard Hospital, Montbeliard; Pitie-Salpetriere Hospital, Paris; Avicenne Hospital, Bobigny) were identified as having oral involvement related to sarcoidosis. Concerning these 12 patients, a diagnosis of sarcoidosis was made by their referring physician between 1993 and 2008. A database combining the main characteristics of sarcoid patients exists in the last centre. In this institution, oral symptoms are not systematically searched and are reported like other rare manifestations, as 'other localization'. Complete information was obtained from the hospital and the referring physician, and retrospectively evaluated in 2010 by one of the authors (JL), using a standardized form.

Patients were included if they met four criteria: (i) symptomatic oral manifestation; (ii) clinical and radiological features compatible with a diagnosis of systemic sarcoidosis; (iii) histological confirmation of non-caseating granuloma in the soft tissues of the oral cavity; and (iv) exclusion of other causes of oral granulomatosis supported by histology of oral tissue biopsy negative for fungus (using Grocott stain) and acid-fast bacilli, and no clinical evidence of another disorder associated with granulomatosis including Wegener granulomatosis, Crohn's disease, tuberculosis, histoplasmosis and syphilis. We did not include patients with intraosseous jaw, salivary glands and trigeminal nerve sarcoidosis.

Medical records were examined for age, gender, race, age at diagnosis, initial and oral symptoms, chest X-ray, pulmonary function tests and serum angiotensin-converting-enzyme (ACE). Special attention was paid to major features indicative of a diagnosis of systemic sarcoidosis. According to the recommendations of Baughman *et al.*,[18] a diagnosis of systemic sarcoidosis was established by means of the following criteria: (i) the presence of granuloma in a biopsy specimen without evidence of another cause of granuloma, together with clinical features suggesting sarcoidosis, such as bilateral hilar lymphadenopathy on chest radiography, erythema nodosum, uveitis and maculopapular skin lesions; and (ii) in the absence of biopsy material, the presence previously mentioned of clinical features and additional features highly consistent with sarcoidosis, such as raised concentration of ACE, bronchoalveolar lavage fluid lymphocytosis, suggestive abnormal gallium scan, and lupus pernio. Pulmonary sarcoid disease on chest X-ray was divided into five stages: Stage 0: no involvement; Stage I: isolated hilar

adenopathy; Stage II: hilar lymphadenopathy with parenchymal infiltrates; Stage III: isolated parenchymal infiltrates; and Stage IV: fibrosis.

We studied the treatment at time of diagnosis of oral sarcoidosis and subsequent management, including surgical excision and medical treatment. The initial treatment was defined as the one performed within 3 months after oral sarcoidosis diagnosis. Concerning the outcome of oral sarcoidosis, stability means that the lesion did not spread and that no other lesion appeared. Oral manifestation improving without complete recovery (size reduction of the lesion or the lesion disappearing with persistent discomfort) corresponds to partial remission. We used the term of 'complete remission' when patients exhibited neither symptoms nor clinical, biological or radiological features of sarcoidosis at the end of follow-up.

Comparison with patients presenting extra-buccal sarcoidosis

Patients with oral sarcoidosis were compared with control subjects presenting a systemic sarcoidosis but no oral manifestations. Patients of the control group were randomly selected among 298 incident cases of histologically proved sarcoidosis hospitalized in the Lyon University Hospital between 2002 and 2006. Each patient with oral sarcoidosis was matched with four controls.

Statistical analysis was performed using the IBM SPSS Statistics 19.0 (IBM Corporation, Somers, USA). Categorical variables were tested by Chi-square test or Fisher's exact test as appropriate. Averages were compared between groups by using the Student *t*-test as appropriate. For the percentage calculation of each variable, the number of missing values was excluded from the denominator.

Results

Physical characteristics and clinical features (Table 1)

Twelve cases were included: 9 women (75%) and 3 men (25%). At time of sarcoidosis, they ranged from 20 to 75 years old (average age: 38 years). Of the 12 patients, 8 were of Caucasian origin (67%), 3 originated from Maghreb (25%) and 1 from South Africa (8%). In seven cases (58%), oral involvement was the presenting manifestation of sarcoidosis. Concerning the five remaining patients, oral involvement occurred within 5 years after sarcoidosis diagnosis (average time: 2.8 years). The diagnosis of oral involvement related to sarcoidosis was made either by specialists of internal medicine, pneumologists, dentists or general practitioners.

Clinical presentations of oral sarcoidosis were nodules ($n=7$) or ulcers ($n=5$), either solitary ($n=11$) or multiple ($n=1$). A severe form occurred in one patient with a palate perforation and collapse (Patient 8). The tongue was the commonest site affected with four cases (Figure 1), followed by lips ($n=3$), oral mucosa ($n=2$), palate ($n=2$) (Figure 2) and gingiva ($n=1$). In the patient with multiple site involvement (Patient 2), lesions were localized on the hard palate, uvula and pharynx.

All patients were found to have other systemic clinical involvement allowing confirmation of sarcoidosis diagnosis, including bilateral hilar lymphadenopathy and/or pulmonary involvement in nine patients (6 patients with radiologic Stage I and 3 patients with Stage II). Ten patients with oral sarcoidosis (83%) had extra-respiratory clinical manifestations at diagnosis or during follow-up. The most frequent were salivary glands ($n=3$), spleen ($n=3$), skin ($n=3$), lacrimal glands ($n=2$), upper airway tract ($n=2$), arthralgia ($n=2$), cervical lymphadenopathy ($n=2$) and liver ($n=1$). Severe localizations such as lupus pernio and sinonasal perforation were observed in one case (Patient 2). One patient (Patient 10) presented an asymptomatic sarcoid myocardiopathy detected by thallium scintigraphy.

Spirometry was performed in 10 patients and showed normal lung function in nine cases. The last one presented an airway obstructive syndrome (Patient 2). Serum ACE level was elevated in three patients (27%). Biopsy of the oral cavity lesion was performed in 10 patients and showed non-caseating epithelioid granulomas with giant cells in all cases. Of these 10 patients, 6 also had extra-oral biopsy proving sarcoidosis characterized in bronchi ($n=1$), cervical ($n=1$) and mediastinal lymph nodes ($n=1$), skin ($n=1$), epiglottis ($n=1$) and conjunctiva ($n=1$). The diagnosis of sarcoidosis was made by ethmoid and nasal mucosae biopsies in the two remaining patients. In all patients, there was no evidence for a differential diagnosis of oral sarcoidosis.

Treatment and outcome (Table 2)

Initial treatment

At the time of the oral involvement diagnosis, none of the five patients with known sarcoidosis were receiving a treatment.

Multiple methods were employed for the initial treatment of oral sarcoidosis ranging from no treatment ($n=3$), surgical excision ($n=3$), hydroxychloroquine ($n=3$), to oral prednisone (from 20 mg/day to 1 mg/kg/day) ($n=7$). Of the 7 patients treated with

Table 1 Clinical, biological, radiologic and histopathological features in patients with oral manifestations of sarcoidosis

	Age at diagnosis (year)/Sex Race	Oral localization	Initial manifestation	Other organs involved	Angiotensin-converting-enzyme	Stage on chest radiography	Histological confirmation (location)
Case 1	24/F Caucasian	Bullous lesion of the tongue	Yes	Mediastinal adenopathy Pulmonary	N	II	Yes (tongue)
Case 2	43/F North African	Multiple lesions: - hard palate - uvula - pharyngeal ulcerations	No (3 years after diagnosis)	Mediastinal adenopathy Lupus pernio Cutaneous lesions (plaques) of the arms Sinonasal lesions (septal perforation, crusted rhinitis) Arthralgia	High	I	Yes (nasal mucosae)
Case 3	26/M Caucasian	Gingivae	Yes	Multiple conjunctival nodules Cervical adenopathy	N	0	Yes (gingivae, conjunctival nodule)
Case 4	75/M Caucasian	Lingual nodule	Yes	Cervical adenopathy Left submandibular gland involvement	N	0	Yes (tongue and cervical adenopathy)
Case 5	43/F North African	Lesion of lower lip mucosa	No (2 years after diagnosis)	Löfgren syndrome Splenomegaly	High	I	Yes (lip)
Case 6	42/F Caucasian	Lingual ulceration Macroglossia	Yes	Mediastinal adenopathy	N	I	Yes (tongue)
Case 7	33/M Caucasian	Cystic lesion of the floor of mouth	Yes	Mediastinal adenopathy Pulmonary	N	II	Yes (floor of the mouth, bronchus)
Case 8	28/F North African	Collapse of palate, palatine perforation	No (4 years after diagnosis)	Mediastinal adenopathy Lacrimal glands involvement Salivary glands involvement	NA	I	Yes (ethmoid)
Case 9	44/F South African	Cystic labial lesion	No (5 years after diagnosis)	Mediastinal adenopathy Sarcoids Arthralgia Splenomegaly Salivary glands involvement (Wharton duct)	High	I	Yes (lip and mediastinal adenopathy)
Case 10	20/F Caucasian	Labial ulceration	Yes	Epiglottic lesion Pulmonary Mediastinal adenopathy Hepatosplenomegaly	N	II	Yes (lip and epiglottis)
Case 11	30/F Caucasian	Nodule of oral mucosa	No (a few weeks after diagnosis)	Unilateral lachrymal swelling	N	0	Yes (oral mucosae)
Case 12	48/F Caucasian	Lingual nodule	Yes	Mediastinal adenopathy Sarcoids	N	I	Yes (tongue, skin)

F: female. M: male. N: normal. NA: not available.

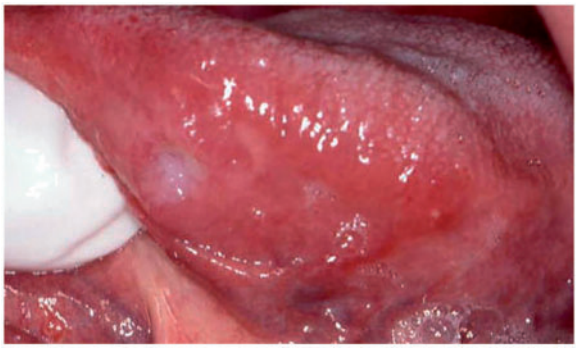

Figure 1. Patient 4: clinical presentation of oral sarcoidosis showing a whitish lesion involving the left side of inferior part of the tongue.

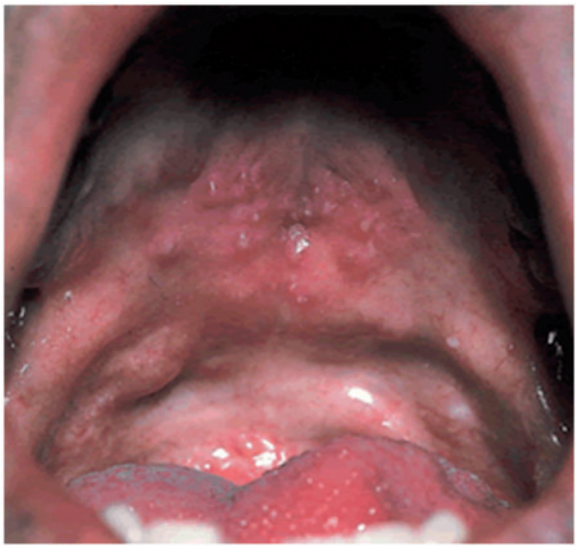

Figure 2. Patient 2: clinical presentation of oral sarcoidosis of the hard palate showing multiple nodules with a whitish central base.

corticosteroids, 4 received other treatments including: hydroxychloroquine ($n=2$), methotrexate ($n=2$), local corticosteroids ($n=1$) and surgical excision ($n=1$).

A clinical improvement of oral sarcoidosis was observed in 11 patients (92%). The last patient (Patient 9) did not receive any treatment because he presented only a small labial lesion without discomfort and was stable during follow-up. Among the 11 patients with clinical improvement, remission was observed in 8 patients (partial [$n=3$] or complete [$n=5$]) and 3 patients (27%) relapsed. The relapse occurred after corticosteroid withdrawal ($n=2$) (1 and 7 months after corticosteroids withdrawal for Patient 3 and 1 respectively), and after 12 months during therapy in the last patient (Patient 10) while he was treated with prednisone (12 mg/day) and hydroxychloroquine (400 mg/day). Oral recurrences involved the tongue ($n=1$), gingivae ($n=1$) and lip ($n=1$), and occurred without extra-buccal relapse. Extra-buccal symptoms of relapse (arthralgia, skin and lacrimal glands) were identified in three patients who presented a buccal remission.

Subsequent treatment

The three patients who relapsed with oral symptoms received a subsequent treatment. It consisted of corticosteroid resumption (from 10 mg/day to 0.5 mg/kg/day), only in one patient (Patient 3), combined with doxycycline in another patient (Patient 1) and combined with hydroxychloroquine continuation in the last patient (Patient 10). After this second-line treatment, 2 out of these 3 patients (Patients 3 and 10) presented a complete remission of oral and extra-buccal sarcoidosis, while corticosteroids allowed stability of oral and extra-buccal manifestations in the last patient (Patient 1). In the latter case, doxycycline was stopped because of its ineffectiveness.

Out of the 3 patients who presented a partial remission after the initial treatment, 1 patient (Patient 2) experienced a recurrence of arthralgia. Corticosteroid treatment resulted in a partial remission of his multiple oral lesions. Another patient (Patient 4) did not receive any subsequent treatment because his lingual lesion caused moderate discomfort and other sarcoidosis manifestations did not require specific therapy. Methotrexate was continued in the third patient (Patient 8) who presented severe palatine involvement. At the end of follow-up, a partial remission of oral sarcoidosis was observed in these three patients after the second-line treatment.

Out of the 5 patients free of oral manifestations after the initial treatment, 2 patients (Patients 5 and 11) experienced a relapse of extra-buccal manifestations and received a subsequent therapy. The first patient presenting cutaneous nodules was successfully treated with antimalarial drugs. The second experienced a lacrimal relapse 4 months after corticosteroid withdrawal, and received a combination of corticosteroids 1 mg/kg/day and hydroxychloroquine which led to complete remission.

Finally, after a mean duration of follow-up of 6 years (range: 1–13 years), complete ($n=7$) or partial ($n=3$) remission of oral manifestations was achieved in 10 patients, while stability was observed in the 2 remaining cases. At the end of follow-up, 7 patients were not receiving any treatment while 5 were under specific treatment for sarcoidosis. Four of them were receiving corticosteroids at low dose (range: 3–7 mg/day) and the last was receiving

Table 2 Treatment and outcome of oral involvement in patients with sarcoidosis

Patients	Initial treatment (duration)	Outcome after initial treatment	Subsequent treatment (duration)	Final outcome		Treatment at the end of follow-up	Duration of follow-up (years)
				Oral manifestation	Other manifestations		
Case 1	- Systemic CT 0.5 mg/kg/day (5 months) - Hydroxychloroquine (9 months)	Relapse 7 months after CT stop	- Systemic CT 10 mg/day - Doxycycline	Stability	Stability	Systemic CT 5 mg/day	2
Case 2	- Systemic CT 20 mg/day (2 years) - Methotrexate 20 mg/week	→ Partial remission → No effect	- Systemic CT (for relapse of arthralgia)	Partial remission	Partial remission	Systemic CT	12
Case 3	Systemic CT 0.5 mg/kg/day (1 year)	Relapse 1 month after CT stop	Systemic CT 10 mg/day (3 years)	Complete remission	Complete remission	0	5
Case 4	Surgical excision	Partial remission	–	Partial remission (with local moderate discomfort)	Stability	0	4
Case 5	- Hydroxychloroquine /Chloroquine (1 year) - Surgical excision	Complete remission	- Hydroxychloroquine/ Chloroquine (for cutaneous nodules) (2 years)	Complete remission	Complete remission	0	6
Case 6	Systemic CT 20 mg/day	Complete remission	–	Complete remission	Complete remission	0	1
Case 7	0	Complete remission	–	Complete remission	Complete remission	0	6
Case 8	- Local CT - Surgical excision - Systemic CT 1 mg/kg/day (2 years) - Methotrexate 15 mg/week	→ Partial remission → Partial remission → Partial remission → Partial remission	Methotrexate continuation	Partial remission	Complete remission	Methotrexate 15 mg/week	6
Case 9	0	Stability	–	Stability	Stability	0	2
Case 10	- Systemic CT 0.5 mg/kg/day (13 years) - Hydroxychloroquine 400 mg/day (3 years)	Relapse after 12 months with CT 12 mg/day and hydroxychloroquine	- Systemic CT 0.5 mg/kg/day - Hydroxychloroquine 400 mg/day continuation (for epiglottic relapse and corticodependence)	Complete remission	Complete remission	Systemic CT 7 mg/day	13
Case 11	Systemic CT 1 mg/kg/day (1 year)	Complete remission	Systemic CT 1 mg/kg/day and Hydroxychloroquine (for lacrimal relapse 4 months after CT stop)	Complete remission	Complete remission	Systemic CT 3 mg/day	4
Case 12	0	Complete remission	–	Complete remission	Stability of mediastinal adenopathy	0	12

CT: corticosteroid therapy. 0: no treatment.
If indicated, the subsequent treatment is justified by another clinical manifestation than oral manifestation.

methotrexate 15 mg/week. Among these 5 patients, only 2 required a specific treatment for oral sarcoidosis: 1 patient (Patient 1) received corticosteroids (5 mg/day) allowing stability of her lingual lesion; another patient (Patient 8) was treated with methotrexate (15 mg/week) in order to maintain partial remission of her palatine involvement, while extrabuccal manifestations were in complete remission.

Comparison between patients with oral sarcoidosis and sarcoid controls

These results are summarized in Tables 3 and 4. The two groups were statistically similar in terms of gender, ethnic and racial distribution, initial chest radiographic stage, pulmonary function test, clinical outcome and treatment. Patients presenting oral manifestations of sarcoidosis were significantly younger than patients without buccal involvement (38 vs. 46 years, $P=0.049$). Clinical features were significantly different between the 2 groups concerning the frequency of upper airway tract (16% vs. 0%, $P=0.012$) and lacrimal and salivary glands (33% vs. 6%, $P=0.009$) involvement, which were higher in the oral sarcoidosis group. On the contrary, the frequency of increased ACE was higher in the control group (78% vs. 27%, $P=0.002$).

Treatment and clinical outcome of the two groups are summarized in Table 4. The proportion of patients receiving a systemic treatment was similar in the two groups. Concerning the proportion of patients receiving oral corticosteroids, immunosuppressants or immunomodulatory agents as initial treatment, there was no difference between the two groups. The mean follow-up duration was 73 months in the oral sarcoidosis group and 97 months in the control group. Recovery, defined as the disappearance of all sarcoidosis symptoms and the absence of recurrence with no treatment for at least 6 months, occurred in five patients (41%) with oral manifestations and 17 patients (35%) without buccal involvement of sarcoidosis, and this difference was not statistically significant.

Table 3 Comparison of patients with oral sarcoidosis and sarcoid controls without oral involvement

	Patients with oral sarcoidosis ($n=12$) No (%)	Controls ($n=48$)	*P*-value
Age at diagnosis, years (mean ± SD)	38 ± 15	46 ± 19	0.049
Male	3 (25)	19 (40)	0.348
Race:			
Caucasian	8 (67)	33 (69)	0.940
North African	3 (25)	10 (21)	
Black	1 (8)	5 (10)	
Organ Involvement:			
Mediastinal Lymph Nodes	9 (75)	31 (66)	0.550
Lung	3 (25)	18 (38)	0.391
Peripheral Lymph Nodes	2 (16)	6 (12)	0.655
Salivary and Lacrimal glands	4 (33)	3 (6)	0.009
Specific Skin lesions	3 (25)	12 (25)	1
Erythema nodosa	1 (8)	5 (10)	0.830
Upper Airway tract	2 (16)	0 (0)	0.037
Arthralgia	2 (16)	3 (6)	0.243
Uveitis	0 (0)	10 (21)	0.083
Heart	0 (0)	0 (0)	
Central Nervous system	0 (0)	4 (8)	0.301
Peripheral Nervous System	0 (0)	1 (2)	0.800
High ACE	3 (27)	28 (78)	0.002
Chest radiography:			
0	3 (25)	9 (19)	0.556
I	6 (50)	20 (43)	
II	3 (25)	14 (24)	
III	0	7 (15)	
IV	0	0	
Spirometry:			
- vital capacity			
Normal	10 (100)	27 (73)	0.180
50–70%	0	6 (16)	
30–50%	0	4 (11)	
- FEV1/VC ratio			
Normal	9 (90)	20 (54)	0.111
50–70%	1 (10)	13 (35)	
<50%	0	4 (11)	
- Low diffusion capacity (DLCO)	0	4 (12)	0.240

FEV1/VC ratio: forced expiratory volume in 1 s/vital capacity. SD: standard deviation.

Discussion

Sarcoidosis is a systemic granulomatous disease rarely affecting the oral cavity and not permitting most case reports found in literature to involve more than 1 or 2 patients.[8,10,12,13] Including our 12 cases, 70 cases have been reported in the literature (Table 5). No study has prospectively assessed the prevalence of oral involvement in a cohort of sarcoidosis patients. Thanks to existing databases, we assessed oral sarcoidosis prevalence in one referral department taking part in this study. Among 3000 cases recruited in this tertiary centre during a period of 21 years, one well-documented oral sarcoidosis case was identified.

Our study, which is the largest ever published on this topic, provides interesting insights on the diagnosis, management and outcome of oral sarcoidosis.

Clinical presentation and diagnosis

In most cases, oral lesions occur in patients presenting a chronic multisystemic sarcoidosis,[14] and are

Table 4 Comparison of patients with oral sarcoidosis and sarcoid controls without buccal involvement: clinical course and treatment

	Patients with oral sarcoidosis ($n=12$) No. (%)	Controls ($n=48$) No. (%)	*P*-value
Follow-up in months (mean ± SD)	73 ± 49	97 ± 78	0.078
Systemic treatment	8 (67)	38 (79)	0.360
Initial treatment with oral steroids	7 (58)	35 (73)	0.324
Initial treatment with immuno-suppressive or -modulatory agents	5 (42)	13 (27)	0.324
Recovery* (mean ± SD)	5 (41)	17 (35)	0.688

*Recovery was defined by the disappearance of all sarcoidosis symptoms and the absence of recurrence with no treatment for at least 6 months.

often the initial manifestation of the disease. In our study, oral involvement revealed sarcoidosis in 58% of cases, similar to findings of the literature ranging from 33%[8] to 58%.[10] These data suggest that mouth examination should be systematically performed in patients with clinical features compatible with sarcoidosis. Moreover, when confronted with unexplained buccal lesions, a careful physical examination should be performed in order to detect an underlying sarcoidosis.

However, oral manifestations can also appear after a prolonged intermittent corticosteroid therapy and during long-term medical follow-up, suggesting the importance of a close oral follow-up and examination of affected patients, even with systemic control of the disease.[11] In our cohort, five patients with known multisystemic sarcoidosis presented buccal involvement within 5 years after sarcoidosis diagnosis. Even though two out of these patients had previously received a specific treatment for sarcoidosis, none of them were treated at the time of the diagnosis of oral sarcoidosis.

Among the 70 patients with oral sarcoidosis identified in the literature, the average age was 39 years and 33% were men, which is similar to the demography of our 12 patients (mean age, 38 years and men/women ratio, 3/9). Sarcoidosis seems to be diagnosed earlier in patients with oral manifestation in comparison with controls. In the literature review including our 12 cases, most of the patients were of Caucasian origin (52%), 29% were Black, 11% North African, 5% Hispanic and 4% Asian.

Clinically, the disease can affect any site of the mouth. According to the literature review, buccal mucosa has been described as the commonest site affected (30%), followed by gingiva (20%), lips (16%), tongue (16%) and palate (9%). Conversely to these data, tongue and lips were the commonest sites affected in our study. Buccal involvement appears as a non-tender well-circumscribed brownish red or purplish swelling, as papules, or as submucosal nodules that can occasionally either show superficial ulceration or may be symptomatic. Gingival involvement leads to varied clinical presentations including gingival hypertrophy, gingivitis with or without gingival recession and gingivorragia, periodontitis and loosening of teeth.[4,9,11,13,16,19] Lesions are most often solitary, but may be multiple in 10% of cases according to the literature review. In the present study, the clinical presentation was in accordance with these data, as 92% of patients showed a single oral lesion. In one case, buccal manifestations were multifocal, involving hard palate, uvula and pharynx.

Oral sarcoidosis is most often asymptomatic or mildly symptomatic[14] giving great importance to buccal examination which should be systematic and meticulous when confronted with a patient presenting clinical features compatible with a systemic sarcoidosis diagnosis. Moreover, as asymptomatic lesions can disappear after systemic treatment and before the physician notices them, one can hypothesize that oral involvement may be more common than reported.

Demographic features and respiratory function tests did not differ significantly between sarcoid patients with or without oral involvement. Among extra-pulmonary localizations, we found a highly positive association between oral and upper respiratory tract involvement, which was present in 16% of our cases, and lacrimal and salivary glands clinical involvement, which was exhibited by one third of patients with oral sarcoidosis. Upper respiratory tract involvement in sarcoidosis is uncommon,

Table 5 Review of the literature: 70 cases of oral sarcoidosis (adapted from Suresh and Radfar)[8]

Author, year of publication	Age	Sex	Race	Chief complaint	Management
Buccal mucosa (*n* = 21)					
Schroff, 1942[26]	48	F	C	Swelling	–
Campbell, 1944[27]	72	M	–	Loose denture	Biopsy and resolution
Kolas and Roche, 1960[28]	15	M	C	Multiple lumps	Steroids
Orlean and O'Brien, 1966[29]	33	M	B	Swelling	Oxygen
Hobkirk, 1969[30]	30	M	–	Pain	–
Hoggins and Allan, 1969[31]	45	F	–	Swelling	Surgery, radiation
Gold and Sager, 1976[32]	–	–	–	Pain	–
Greet and Sanget, 1977[33]	37	F	C	Swelling	No treatment
Orlian and Birnbaum, 1980[34]	43	F	C	Swelling	Surgery
DeLuke and Scuibba, 1985[35]	35	F	B	Swelling	Steroids
Klesper *et al.*, 1994[36]	16	F	C	Swelling	–
Blinder *et al.*, 1997[37]	43	F	C	Swelling	No treatment
	62	F	C	Nodules	No treatment
Piattelli *et al.*, 1998[2]	44	–	–	Ulcer	–
Jackowski *et al.*, 2005[7]	39	M	C	Mass	Excision
Kasamatsu *et al.*, 2007[10]	71	F	A	Nodule	Spontaneous remission
Khaled *et al.*, 2008[15] (3 patients)					
Bouaziz *et al.*, 2012	33	M	C	Cystic lesion	Spontaneous remission
	30	F	C	Nodule	Steroids
Gingiva (*n* = 14)					
Tillman *et al.*, 1966[38]	18	F	C	Gingivitis	–
Watts, 1968[39]	42	F	–	Hyperplasia	Steroids
Hogan, 1983[40]	37	F	–	Swollen gingiva	Spontaneous remission
Sloan *et al.*, 1983[41]	16	M	C	Hyperplasia	Excision
Altman and Robinson, 1984[42]	36	M	C	Hyperplasia	Steroids
Zakrzewska and Nally, 1985[43]	30	F	C	Gingivitis	–
	33	M	C	Gingivitis	–
Hayter and Robertson, 1988[44]	34	M	–	Ulcers	No treatment
Caudill, 1988[45]	57	F	C	Gingival recession	Surgery
Armstrong *et al.*, 2004[4]	39	F	C	Gingivitis and ulcers	Excision
Antunes *et al.*, 2008[11]	57	F	H	Ulcer	Topical steroids
Aslangul *et al.*, 2008[16]	28	F	–	Gingivitis, hyperplasia	Topical antiseptic
Poate *et al.*, 2008[13]	41	F	B	Swelling	No treatment
Bouaziz *et al.*, 2012	26	M	C	–	Steroids
Palate (*n* = 6)					
Cohen *et al.*, 1981[46]	40	F	B	Multiple nodules	No treatment
Van Maarsseveen *et al.*, 1982[47]	23	M	–	Multiple nodules	No treatment
Hildebrand *et al.*, 1990[48]	36	M	B	Papule	Steroids
Ho and Blair, 2003[49]	58	F	B	Gingival redness	No treatment
Suresh *et al.*, 2004[6]	25	F	B	Swelling	Intralesional steroids
Bouaziz *et al.*, 2012	28	F	NA	Perforation	MTX, steroids
Lip (*n* = 11)					
Calderon *et al.*, 1990[50]	28	F	C	Nodules	Steroids
Bourgeois-Droin *et al.*, 1993[51]	10	F	B	Swelling	–
	5	M	B	Swelling	–
Steinberg and Mueller, 1994[52]	37	M	B	Nodules	Steroids
	28	F	B	Nodules	Surgery
Piattelli *et al.*, 1998[2]	54	M	–	Ulcer and swelling	–
Lowry, 2004[5]	41	M	B	Nodule	Excision
Marcoval and Mana, 2010[17]	66	F	H	Nodule	No treatment
Bouaziz *et al.*, 2012	43	F	NA	Nodule	Excision, hydroxychloroquine
	44	F	B	Cystic lesion	No treatment
	20	F	C	Ulceration	

(continued)

Table 5 Continued

Author, year of publication	Age	Sex	Race	Chief complaint	Management
					Hydroxychloroquine, steroids
Tongue (*n* = 11)					
Tillman *et al.*, 1966[38]	37	M	B	Swelling	Surgery
Van Maarsseveen *et al.*, 1982[47]	69	F	–	Nodule	No treatment
MacLeod *et al.*, 1985[53]	30	F	C	Swelling	Steroids
Mendelsohn *et al.*, 1992[54]	43	M	–	Swelling	–
Soto *et al.*, 1997[55]	56	F	C	Swelling	Steroids
Marie *et al.*, 2008[12]	25	F	C	Ulceration	Steroids
Marcoval and Mana, 2010[17]	53	F	H	Plaque	Hydroxychloroquine
Bouaziz *et al.*, 2012	24	F	C	Bullous lesion	Steroids, hydroxychloroquine
	75	M	C	Nodule	Excision
	42	F	C	Ulceration	Steroids
	48	F	C	Nodule	Spontaneous remission
Multiple sites (*n* = 7)					
Covel, 1954[56]	26	F	–	Multiple ulcers	–
Zakrzewska and Nally, 1985[43]	33	–	B	Multiple ulcers	–
Nagata *et al.*, 1999[57]	32	F	A	Ulcers and swelling	Steroids
Moretti *et al.*, 2007[9]	47	M	C	Gingivitis, gingival recession	Steroids
Poate *et al.*, 2008[13]	43	F	B	Lip and palatal swelling	Intralesional steroids
Kolokotronis *et al.*, 2009[14]	46	F	C	Plaques	–
Bouaziz *et al.*, 2012	43	F	NA	Multiple ulcerations	Steroids, MTX

F: female. M: male. C: Caucasian. B: Black. NA: North African. As: Asian. H: Hispanic.
–: no data available. MTX: methotrexate.
We conducted a computer-assisted (PubMed, National Library of Medicine) search for publications in English and French, up to November 2011 (keywords: sarcoidosis, oral, buccal), in order to identify all cases of oral sarcoidosis. The reference lists of all the articles were scanned for other references not identified in the initial research.

occurring in 2.3% of the 736 patients included in the large epidemiological study A.C.C.E.S.S., recently performed in the USA.[20] The pathogenesis of such associations remains unclear, but the anatomic proximity of these localizations may result from contiguous extension of granulomas. Oral manifestations of sarcoidosis should be carefully searched out when a patient is presenting upper airway tract, lacrimal or salivary glands manifestations of sarcoidosis. Buccal sarcoidosis seems to be not associated with severe manifestations of the disease, as uveitis, nervous system or kidney involvement. Of the 12 patients, only 1 exhibited lupus pernio and sinonasal lesions with septal perforation. One other patient presented an asymptomatic heart involvement, which was only highlighted by thallium scintigraphy.

Concerning biologic tests, ACE level was normal in almost three quarters of patients with oral sarcoidosis. ACE is produced by the epithelioid cells of granulomatous lesions and thus may be elevated in the serum of sarcoid patients. Some authors have previously suggested that a low ACE level may be correlated with a low mass of sarcoid granuloma.[21] Our study may suggest that patients with oral sarcoidosis may have a lower mass of sarcoid granuloma than patients without such localization.

In some cases, sarcoidosis is limited to the buccal cavity in an otherwise healthy patient. For instance, Aslangul et al described the clinical history of a woman presenting a chronic gingival hypertrophy and no other manifestations of sarcoidosis.[16] In these cases of isolated oral manifestations, the literature reveals no consensus concerning differential diagnosis with orofacial granulomatosis (OFG). This widely-described entity of unknown aetiology corresponds to persistent enlargement of soft tissues of the oral and maxillofacial region, characterized histologically by non-caseating granulomatous inflammation.[22] The classic presentation is that of a non-tender recurrent labial swelling that may sometimes persist; other manifestations include angular cheilitis, vertical fissures of the lips, mucosal ulcerations or tags, and lingua plicata. The histological features of OFG are indistinguishable from sarcoidosis or Crohn's disease, raising the question of a continuum existing between these different entities.

The diagnosis of sarcoidosis is established with compatible clinical, radiological and histopathological features associated with the exclusion of known causes of granuloma.[18] In this setting of oral lesions, differential diagnosis must be made with foreign body granulomas, infections (including tuberculosis, syphilis, leprosy, cat-scratch disease and mycosis), Crohn's disease, Wegener's disease and OFG.[23] Special stains and cultures must be performed to exclude fungi or tubercle bacilli infections. In our study, none of the 12 patients exhibited clinical, biological or histopathological features for a differential diagnosis of sarcoidosis.

Treatment

Scientific societies have identified several conditions requiring treatment[24] in patients with systemic sarcoidosis, including symptomatic pulmonary involvement (Stage II–III), neurological, renal, cardiac, cutaneous manifestation affecting the face and hypercalcaemia. Concerning oral sarcoidosis treatment, the available information is poor and mainly comes from scattered case reports. Not all cases of oral sarcoidosis require treatment because the symptoms tend to resolve spontaneously within 2 years in ~60% of patients.[10] The choice of treatment mainly depends on severity and extent of the disease. A good buccal hygiene is required anyway. When lesions are localized, surgical excision is commonly employed, allowing both histopathological confirmation of sarcoidosis and treatment. When medical therapy is necessary, systemic corticosteroids are considered the mainstay of treatment, alone or in association with hydroxychloroquine, doxycycline or immunosuppressive drugs such as methotrexate.

Among the 70 cases of oral sarcoidosis in the literature review, 52 cases are available with treatment data: systemic corticosteroid therapy was the most commonly employed treatment ($n=19$, 37%), followed by no specific treatment ($n=15$, 29%) and surgical excision and/or curettage ($n=11$, 21%). Some authors have suggested that steroid therapy should be considered in patients with painful and progressive lesions associated with multivisceral and severe sarcoidosis.[12] In our study, 3 patients did not receive any treatment (25%) and 2 of them recovered spontaneously (17%), while the last one had a non-severe and stable lesion. On the other hand, 9 patients required a specific treatment for sarcoidosis. Seven of them (58%) were given steroids for symptomatic oral lesions or other localizations of sarcoidosis. Prednisone was efficient in all patients. However, 3 patients (25%) experienced oral relapses: 2 patients had a single recurrence after the discontinuation of steroids and one patient had multiple recurrences on steroids. We did not observe any particular clinical presentation associated with relapse, partial remission or steroid dependence.

Anti-malarial drugs such as hydroxychloroquine are considered especially useful in the treatment of cutaneous and mucosal sarcoidosis, including nasosinusal and laryngeal sarcoidosis.[25] It showed benefit in only 1 out of our 3 patients, in association with surgical excision. Methotrexate is the most used immunosuppressant for refractory disease or for its steroid-sparing effects, and appeared to be efficient in 1 out of our 2 patients who received it. Other therapeutic methods are described in literature: in their review, Marie *et al.* reported the use of minocycline in three patients.[12] In the literature review, oxygen was used in one patient in 1966, and local steroids (intralesional injections or topical) were reported in three cases. However, these therapeutic options are chosen selectively in particular cases of limited lesions and local procedures are ineffective for the treatment of multisystemic sarcoidosis.

On the last examination, most of our patients were in remission (83%) or had a mild and stable disease without any treatment (8%). Five patients were still receiving a specific sarcoidosis therapy: 3 patients with remission of oral lesions were treated for extra-buccal manifestations (joint, epiglottic and lacrimal involvement), while only 2 patients (17%) were specifically treated for their oral sarcoidosis (tongue and palate involvement). Out of them, one patient with a buccal lesion in partial remission was still receiving methotrexate (15 mg/week) because of a severe initial oral manifestation. The other patient presented a buccal involvement requiring low dose of corticosteroids (5 mg/day).

Our study has some limitations, including the ones inherent to all retrospective observational cohort studies. Secondly, a small number of subjects were included because of the infrequency of oral localization in sarcoidosis. The third limitation is that cases were provided by physician experts in sarcoidosis and belonging to a nationwide group. Therefore, patients included in our study are expected to be more severe on average than those encountered in a primary setting, so our results may be applied generally to secondary or tertiary sarcoidosis practices. Further studies performed by other institutions in different countries are mandatory to confirm our results.

In conclusion, our study reinforces the possibility of an unusual presentation of sarcoidosis. According to previous reports, oral lesions were the presenting manifestation of sarcoidosis in almost two-thirds of our patients. In the literature, buccal mucosa and gingiva are the most frequently reported oral

localizations. Conversely to these data, tongue and lips were the commonest sites affected in our study. Oral involvement was associated with upper respiratory tract sarcoidosis and lacrimal and salivary glands involvement, suggesting a facial tropism of the disease in such patients. Serum ACE level was often normal in patients with oral manifestations of sarcoidosis. Treatment modalities of oral sarcoidosis range from observation in asymptomatic patients, since lesions may spontaneously disappear, to immunosuppressants. Presentation as localized swelling may be treated with simple surgical excision, while gingival hyperplasia and gingivitis may be controlled by scaling, polishing and strict good oral hygiene. Steroids should be considered in cases of painful and progressive lesions. Methotrexate seems to be the preferred treatment for severe forms of oral sarcoidosis or as a steroid sparing agent. Oral relapses occur in one quarter of cases but usually resolve with treatment.

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