# OTORHINOLARYNGOLOGICAL MANIFESTATIONS OF SYSTEMIC DISORDERS

# LES MANIFESTATIONS OTO-RHINO-LARYNGOLOGIQUES DES MALADIES SYSTÉMIQUES

S. Mezri[1,2], S. Sayhi[5,2], C. Zitouni[1,2], S. Bessioud[1,2], W. Thabet[3,4], K. Akkari[1,2]

[1] Department of Otorhinolaryngology, Military Hospital of Tunis, Tunisia

[2] University of Tunis

[3] Department of Otorhinolaryngology, Tahar Sfar Hospital Mahdia, Tunisia

[4] University of Monastir

[5] Department of Internal Medicine, Military Hospital of Tunis, Tunisia

## ABSTRACT

**Introduction:** Systemic diseases are characterized by multiorgan involvement. Ear-nose-throat (ENT) disorders are among the most common manifestations of systemic diseases. The aim of this study was to describe the epidemiological, clinical, and prognostic features of the ENT manifestations of systemic diseases.

**Methods:** A retrospective study including patients treated in our department (Otorhinolaryngology and Internal medicine) for systemic diseases and presenting ENT manifestations between January 2010 and December 2017.

**Results:** Forty patients were included. The systemic disorders were connective tissue disease (14 cases), sarcoidosis (10 cases). Vasculitis and infiltrative disease were less frequent. The ENT symptoms had revealed the diagnosis in 13 cases , the sinonasal symptoms were the most reported ones (30%). After treatment, 90% of patients had improvement or stabilization of their ENT symptoms. Two patients died from laryngeal dyspnea (amyloidosis) and parotid lymphoma (Sjogren's syndrome).

**Conclusion:** The ENT signs during systemic diseases are polymorphous and often non-pathognomonic. Otorhinolaryngologists should keep in mind systemic diseases when confronted with any ENT manifestations, especially those demonstrating an atypical evolution or accompanied by extra-ENT symptoms.

**Key-words:** ENT, Systemic disorders, Sarcoidosis, Connectivitis, Vascularitis, Granulomatosis.

## RÉSUMÉ

**Introduction:** les maladies systémiques sont caractérisées par l'atteinte simultanée de plusieurs organes. Les atteintes oto-rhino-laryngologiques (ORL) sont assez fréquentes pouvant être révélatrices ou émailler l'évolution de la maladie systémique.

L'objectif de notre étude était de décrire les aspects épidémiologiques, cliniques et pronostiques des manifestations ORL au cours des maladies systémiques.

**Matériels et méthodes:** Nous avons mené une étude rétrospective incluant les patients ayant été pris en charge pour une atteinte de la sphère ORL en rapport avec une maladie systémique durant la période allant de Janvier 2010 à décembre 2017.

**Résultats:** Quarante (40) patients ont été inclus. Il s'agissait essentiellement de connectivites (14 cas) et de sarcoïdose (10 cas). Les vascularites et les maladies infiltrantes étaient moins fréquentes.

Les symptômes ORL étaient révélateurs de la maladie dans 13 cas avec une prédominance des signes rhino-sinusiens (30%). L'évolution était marquée par l'amélioration des symptômes dans 90% des cas.

Deux décès ont été rapportés à la suite d'une détresse respiratoire secondaire à une amylose laryngée dans un cas et à une transformation lymphomateuse d'une maladie de Sjögren dans un cas.

**Conclusion:** Les manifestations ORL au cours des maladies systémiques sont polymorphes et souvent non pathognomoniques. Les praticiens, notamment de premières lignes, ORL et internistes doivent garder à l'esprit la possibilité de cette expression chez les patients ayant une symptomatologie et/ou une évolution atypique de leur maladie.

**Mots-clés:** Oto-rhino-laryngologie, Maladies systémiques, Sarcoïdose, Connectivites, Vascularites, Granulomatoses.

Corresponding author: Bessioud Salma
E-mail:salmabessioud@gmail.com

## INTRODUCTION:

Systemic diseases are a wide range of nosological disorders. Multiorgan involvement as well as immune dysfunction are the common signature of these affections. Ear-nose-throat (ENT) manifestation is among the most common manifestations of systemic illnesses. Some systemic diseases may be revealed by ENT manifestations, but at the same time these symptoms can often be misleading. The lack of specificity can lead to misdiagnosis and/or delayed diagnosis(1).On the other hand early management is so important since it can prevent the onset of more severe systemic manifestations mostly characterized by renal, cardiac or neurological impairment, which may affect the functional and/or vital prognosis(1).

ENT involvement is frequent in some systemic disorders, such as sarcoidosis, atrophic polychondritis, or certain ANCA vasculitis: granulomatosis with polyangiitis (Wegener's granulomatosis) and Churg-Strauss syndrome. For other diseases, ENT involvement is rarer but may reveal the disease. Thus, cooperation between ENT specialists and internists is essential to optimize the prognosis of these patients.

The aim of this study is to describe the epidemiological, clinical, and prognostic features of the ENT manifestations of systemic diseases.

## METHODS:

A retrospective study including patients treated in our department (Otorhinolaryngology and Internal medicine, Military hospital of Tunis) for systemic diseases and presenting ENT manifestations between January 2010 and December 2017. The conditions of the Helsinki Declaration were satisfied.

## RESULTS:

Forty patients were included. The age of patients ranged from 7 to 73 years, with an average of 46.5 years. In our series, 9 patients (22%) had a history of a systemic disease. Twelve patients (33%) had an ENT history which included (Multinodular thyroid goiter, allergic rhinitis, recurrent rhinosinusitis, recurrent tonsillitis, otitis media with effusion).

The onset of ENT symptoms was insidious in 33 patients (83%). On the other hand, in 8 cases (20%), ENT organ involvement was a symptomatic and was discovered during a systematic examination of the ENT sphere in connection with another otolaryngological lesion.

ENT signs reported by the patients were dominated by sinonasal symptoms in 12 cases (30%), mostly presented by chronic nasal obstruction found in 11 patients (28%), followed by cervical swelling in 8 patients (20%).

In our study, all ENT organs were affected by systemic disease. The ENT involvement was present at the time of diagnosis of the underlying systemic disease in 31 cases (78%) and had revealed the diagnosis in 13 cases (42%).Salivary glandular tissue (including accessory salivary glands and main salivary glands) was the most affected (33%). It was followed by sinonasal cavities (30%), cervical lymph node (30%), larynx (17%), pharynx (15%), oral cavity (10%), external ear (7%), the VII and VIII cranial pairs (7%), face (5%) and thyroid gland (3%).

Extra-ENT signs were observed in 29 patients (73%), mostly represented by general signs in 17 patients (43%) (Fever in 11 patients (28%), deterioration of general condition in 15 patients (38%)) and inflammatory arthralgia in 64% of cases. Other functional signs are summarized in Table I.

**Table I: Extra-ENT manifestations**

| organ | Symptomatology |
|---|---|
| Respiratory system (n=11) | Effort dyspnea n=5(13%)<br>Chronic bronchitis n=2(5%)<br>Chronic dry cough n=2(5%)<br>Hemoptysis n=1(3%)<br>Wheezing dyspnea n=1(3%) |
| Skin (n=6) | Generalized rash n=1(3 %)<br>Erythema nodosum n=1(3 %)<br>Subcutaneous nodules n=1(3 %)<br>Cutaneous atrophy and sclerosis n=1(3 %)<br>Bullous lesions n=1(3 %) |
| Kidney (n=3) | Macroscopic hematuria 2(5 %)<br>Microscopic hematuria 1(3 %) |
| CNS (n=2) | Meningeal signs n=1(3 %)<br>Pyramidal syndrome n=1(3 %) |
| Eye (n=2) | Exophthalmos n=1(3 %)<br>Decreased visual acuity and ocular redness n=1(3%) |

The systemic disorders were connective tissue disease (14 cases), sarcoidosis (10 cases), vasculitis (5 cases), infiltrative disease (6 cases), and others (5 cases).

Seven cases (17%) were diagnosed with Sjögren's syndrome: six women and one man with an average age of 48. The ENT involvement occurred during 4 previously known Sjogren's syndrome patients, whereas it preceded disease diagnosis in the other 3 cases.

The symptoms which were constantly noted are Dry eyes, mouth, and nose.

The majority of cases involved the affection of the following ENT tissues: salivary gland (GSA (n=7), parotid gland (n=4), and submandibular gland (n=1) and less frequently the cranial pairs in 2 cases.

Revealing manifestations of ENT involvement were dominated by cervical swelling (n=5), followed by facial asymmetry (n=1) and sudden deafness (n=1). Examination revealed parotid swelling (n=4), submandibular swelling (n=1), and unilateral peripheral facial paralysis (n=1).

An associated extra-ENT manifestation was constantly present in100 % of cases; the most common one was joint involvement, found in 6 patients (85%). One patient was diagnosed with parotid lymphomatous transformation.

Four patients (10%) were diagnosed with chronic

atrophic polychondritis, including three women and one man with an average age of 49. Only one patient had extra-ENT involvement. As for the ENT symptoms, the most common finding was Auricular chondritis (n=3). Two patients had Damage to the laryngeal cartilaginous framework. It was symptomatic of exertional dyspnea in one patient, and subclinical but radiologically discovered in the other. And only one patient reported recurrent nasal chondritis. The search for autoimmune diseases associated with CAP was negative even in the patients with extra-oral involvement.

There was one case of Rheumatoid arthritis (RA) with laryngeal involvement in our series. It involved a woman, who presented with dysphonia. On examination, Unilateral Vocal Fold Immobility due to cricoarytenoid ankylosis was noted. The laryngeal CT scan showed perichondral inflammatory lesions and calcification of the cricoid cartilage.

Systemic scleroderma with ENT localization was found in a 73-year-old patient. Symptoms consisted of xerostomia, odynophagia, and dysphonia. Examination revealed a microstomia with limited mouth opening, microcheilia, and perioral rhagades.

A 33-year-old patient diagnosed with Scleromyositis, presented Velopharyngeal insufficiency with open rhinolalia associated with velopharyngeal musculature deficiency which was revealing mode of muscular involvement.

It was associated with elevated serum muscle enzymes and was followed by the onset of proximal muscular deficit and pulmonary involvement (diffuse interstitial lung disease) symptomatic of a dry cough with exertional dyspnea.

In our series, sarcoidosis represented the most frequent etiology of ENT manifestation, diagnosed in 10 patients (25%). The average age of the patients was 46.5 years, with a clear female predominance (gender ratio M/F=0.25). The average time to diagnosis was 12.8 months. ENT involvement was inaugural of sarcoidosis in almost all cases (n=9). It had various localizations but were dominated essentially by sinonasal involvement. It was limited to a single ENT organ in 6 cases (60%). It involved two ENT organs in 3 cases (30%) and was multiorgan involved in 1 case (10%). Systemic involvement was almost constant, noted in 9 patients (90%); the respiratory system was the most affected in 70%. Elevated blood level of ACE was increased in 3 patients (30%).

Three patients were diagnosed with EGPA (8%): two men and one woman with a mean age of 52 years. An inaugural sinonasal localization of eosinophilic granulomatosis with polyangiitis was found in all cases (n=3), with ENT symptoms preceding systemic manifestations by an average of 8.7 years. All three patients shared the same clinical symptoms. ENT features included nasal obstruction and chronic purulent rhinorrhea, less frequently chronic sinusitis, epistaxis, and anosmia. Facial CT scan showed a common abnormality: a chronic, non-specific inflammatory process of the various sinus cavities. Anatomopathological analysis showed an eosinophilic tissue infiltration in one case , and ANCA were positive in 2 cases, while blood hypereosinophilia was common to all patients.

In our series, granulomatosis with polyangiitis (GPA) was diagnosed in two patients: one man and one woman aged 64 and 34, respectively. ENT symptoms were the first signs of the disease. These were symptoms of chronic rhinosinusitis with episodes of reheating and chronic rhinitis with polyposis. On anterior rhinoscopy, the nasal mucosa was congestive with a granulomatous appearance and nodular turbinate hypertrophy in one case and ulcerative crusting in the other (Figure 1). Nasofibroscopy showed diffuse inflammation extending to the cavum in both cases. ENT manifestations were associated with general signs. Pulmonary involvement was characterized by hemoptysis (n=1) and recurrent bronchitis (n=1), while renal involvement was characterized by macroscopic hematuria and rapidly progressive renal failure.

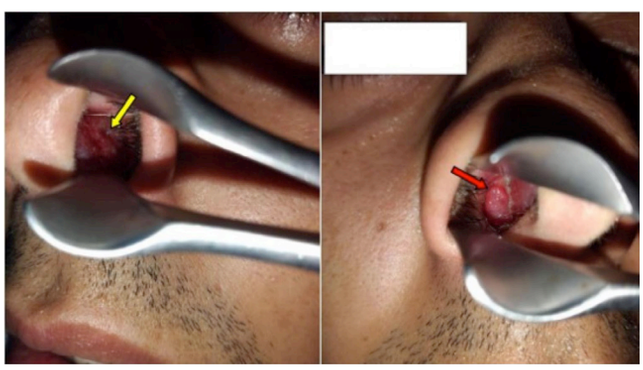

**Figure 1** :Anterior rhinoscopy reveals mucosa (yellow arrow) and nodular turbinate hypertrophy (redarrow).

ENT involvement was found in 4 cases (10%) of Amyloidosis. It involved the larynx (n=2), the thyroid gland (n=1) and was diffuse, affecting all three levels of the pharynx, the larynx, and lymph nodes in the last case. In our series, we haven't noted extra-ENT involvement. In order to rule out systemic involvement, extension work-up and the associated hematological pathologies were negative in all patients. Symptoms included dysphonia with laryngeal dyspnea, goiter and multiple compressive cervical lymph nodes.

ENT involvement in Langerhans cell histiocytosis (LH) was diagnosed in 2 cases (5%): cervical lymph nodes and mandibular bone. The ENT manifestation was the first sign of the disease. It revealed underlying systemic histiocytosis only in 1 of the 2 patients. The first patient, aged 7 with no previous medical history, was admitted to the pediatrics department for central diabetes insipidus related to a hypothalamic tumor associated with cervical lymph nodes. Adenectomy under general anesthesia was performed. The diagnosis was based on the presence of Langerhans cell granuloma, confirmed by positive CD1a immunohistochemical staining. (Figure 2)

The second patient, aged 58 with no previous medical history, presented with mandibular tumefaction with trismus. On examination, there was a fixed solid tumor in the horizontal ramus of the mandible and solid, movable lymph nodes in sector Ib. The Dentascan showed a lytic lesion with pathological fracture (Figure 3). MRI confirmed the aggressive nature of the tumor, with homolateral muscle extension (Figure 4). The patient underwent non interruptive mandibulectomy. Anatomopathological combined with immunohistochemical examination was in favour of LH. The extension work-up was negative.

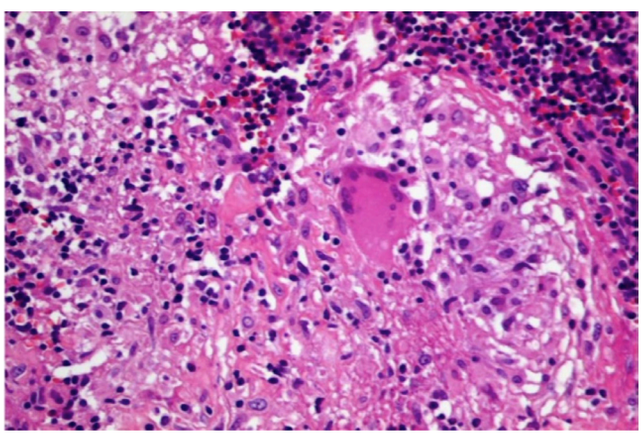

**Figure 2** : pathological examination showing tuberculoid granuloma on lymph node fine-needle aspiration.

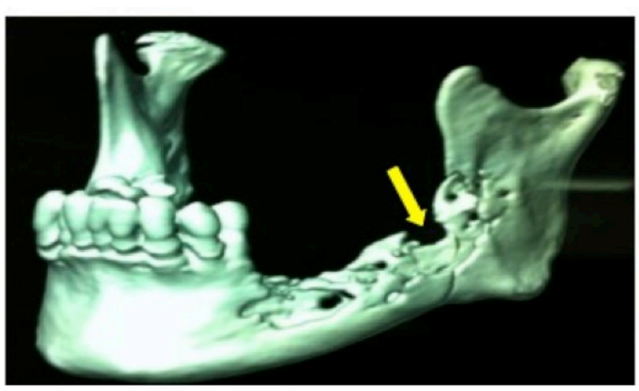

**Figure 3** : Lytic lesion of the left mandibular horizontal ramus with pathological fracture secondary to histyosis X (yellow arrow).

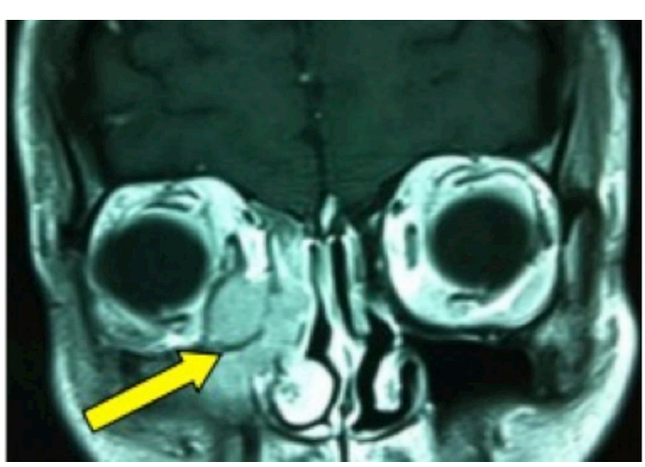

Figure 4: Coronal MRI of the face demonstrates an extra-conal orbital tissue process with a homolateral nasal sinus extension, which is hyperintense on T1 , suggesting Castleman disease.

The others diseases were presented in Table II.

**Table II: Other systemic diseases and ENT manifestations**

| Systemic disease | cases | age | ENT localization | symptoms | Paraclinical tests |
|---|---|---|---|---|---|
| still disease | 2 | 33 | -Oropharynx -cervical lymphnodes | -Fever Polyarthralgias -Skin rash -Odynophagia and dysphagia | -Inflammatory lymphadenopathies on ultrasound -Hyperneutrophilia |
| | | 24 | -Oropharynx | Fever Polyarthralgias | -Hypoyglobulinemia -Hyperleukocytosis predominantly neutrophilic -Macrophage activation syndrome with cholestasis, hyperferritinemia |
| Melkersson-Rosenthal syndrome (MRS) | 1 | 39 | tongue and lips | Recurrent lipswelling | Granulomatous sialadenitis of the salivary glands |
| Castlemandisease | 1 | 49 | Facial mass | suborbital swelling Exophthalmos and lagophthalmos | -Orbital tumor locally extensive (Figure4) -Non-specific histology |
| Pemphigus Vulgaris | 1 | 56 | -Oral cavity and pharyngolarynx | -Lesions mucous membranes erosive -Lesions skin bullous | -Biological inflammatory syndrome. - The bacteriological, mycological examinations ,and AAN were negative |

Patients received either medical treatment or underwent endoscopic sinus surgery, or both. The medical treatment consisted of local corticosteroids and/or systemic corticosteroids and/or immunosuppressive therapy. The duration of medical treatment was variable, ranging from a few months to still continuous treatment. Thirty-two (80%) patients were treated with systemic steroids and no surgical intervention was needed. Ten patients (25%) underwent immunosuppressive therapy. In 8 cases (20 %), endoscopic surgery was performed in addition to medical therapy.

Treatment resulted in remission for 18 patients, accounting for 45% of the cases, but despite receiving appropriate care, 3 patients (7%) had an unfavorable outcome (continued progression of laryngeal amyloidosis resistant to corticosteroid therapy, an increase in the frequency of chondritis flare-ups during exacerbation of microstomia secondary to Scleromyositis. Two patients died from laryngeal dyspnea (amyloidosis) and parotid lymphoma (Sjogren's syndrome).

## DISCUSSION

ENT involvement in systemic diseases is considered to be uncommon. In a study by Knopf and al, they reported 120 cases out of 40,000 patients (0.3%) treated for ENT conditions, from all causes, during the study period. In the same study, only 3% of salivary gland swellings and 4% of cervical lymph node enlargements were linked to systemic diseases (2) .

This contrasts significantly with the study by Iguelouane and collaborators, where ENT manifestations were among the most common clinical presentations of systemic or autoimmune diseases, accounting for 67.5% of patients treated in internal medicine.(3).

This statistic disparity stems from the fact that the

prevalence of ENT involvement in systemic diseases is very variable depending on the underlying disorder. Indeed, some of them have a predominant ENT involvement, such as chronic atrophic polychondritis in which auricular chondritis is present in 90%(4), and granulomatosis with polyangiitis, in which sinonasal manifestation is found in 90% of cases(5).

According to the literature, ENT manifestations in systemic diseases can appear at any age, including in children, but are more commonly seen in adults.

In our study, the highest rates are in the 30 to 59 age group. Comparable to our study, various series have clearly shown the predominance of women. This can be explained by the frequency of systemic diseases in women(6).

Sarcoidosis is a multi-visceral granulomatous disease of unknown cause and the clinical presentation is variable. (7,8).

In our study, the mean age of 45.6 years closely aligns with findings from various series, which report a predilection for ENT sarcoidosis among adults aged between 20 and 40 years (9,10). Furthermore, we observed a significant female predominance within our population, a trend consistent with virtually all studies in this field.

ENT involvement in sarcoidosis is uncommon, occurring in 10 to 15% of all systemic sarcoidosis cases. It typically presents as cervical lymphadenopathy, with pharyngolaryngeal involvement in 1% of cases and naso-sinus involvement in 2%.(2,11).

In our series, sinonasal involvement ranked first among ENT manifestations of sarcoidosis (60%).

While older publications have reported nasosinusal sarcoidosis as a rarity (12,13), several more recent studies align with our findings, suggesting that nasosinusal sarcoidosis is more prevalent, with frequencies ranging from 30% to 69.23%(13–15).

Sjogren's syndrome (SS) is an autoimmune exocrinopathy characterized by progressive and irreversible lymphoplasmacytic infiltration (16) . Retamozo et al estimated that ENT involvement occurs in 1.3% of SS cases. However, in our study group, SS was by far the most common connective tissue disease, accounting for 18% of all etiologies. The most frequent ENT manifestation in SS is parotid swelling.(17)

In our patient, the distribution according to the organs affected was as follows: the parotid gland in 4 cases, the submandibular gland in 1 case, and involvement of the VIIth and VIIIth cranial pairs in 1 case each, in line with the literature .

Chronic atrophic polychondritis (CAP) is characterized by chronic inflammation of cartilage structures, which can result in fibrosis and the destruction of cartilage. (1,18). The features of chronic atrophic polychondritis (CAP) are diverse, but the most common manifestations include chondritis (43%) and nasal chondritis (21%). (19). Furthermore, forty per cent of cases report Cochleovestibular damage(20). In our series, ENT involvements of CAP are, respectively, the ear, nose, and larynx. On top of that, CAP was revealed by ENT manifestations in all our cases, aligning with previous studies.

Granulomatosis with polyangiitis (GPA) is a very rare disease, classified as a systemic necrotizing vasculitis. In addition to pulmonary and renal symptoms, ENT involvement is one of the most frequent manifestations. GPA can affect various areas in the ENT region, including the nose, sinuses, ears, larynx, tonsils, oral cavity, cranial nerves, and parotid glands (21,22).

Often indicative of the disease in 70 to 100% of cases according to Greco and al(23), and in 80% according to Rogister and al [40]. Nasosinus involvement is the most frequent ENT manifestation (23,24).

In our study, we reported one single case of rheumatoid arthritis with laryngeal manifestation. In the ENT field, the majority of cases are articular. Laryngeal involvement is the most frequent and potentially the most serious, occurring in 25 to 35% of cases(1).

ENT involvement in scleroderma (excluding cutaneous and facial sclerosis) is poorly described in the literature. In our series, we report 2 distinct cases: advanced oropharyngeal involvement by systemic scleroderma and pharyngolaryngeal involvement during scleromyositis revealed by velar insufficiency. In a review of the literature, Hadj Said and al counted a total of 1187 orofacial manifestations associated with scleroderma predominantly affecting women (84.5%), with an average age of 40.2 years (25). Involvement of the masticatory and velar musculature has also been reported, and can cause trismus and velar insufficiency (25), as in our patient's case.

Granulomatosis with polyangiitis(GPA) is a necrotizing systemic vasculitis of small vessels. It is the most common vasculitis in the ENT setting, and conversely, several publications have demonstrated the frequency of ENT localization in this disease, which was included as one of six diagnostic criteria in the former American College of Rheumatology ACR 1990 classification(26). As far as ENT involvement is concerned, the nose and sinuses are the most affected by GPA, accounting for up to 100% of patients(27,28). Allergic rhinitis is common (70%) in the initial phase of the disease(6,29) causing nasal obstruction, sinusitis and nasal polyposis (6). In all our patients, sinonasal involvement was inaugural, unifocal, and semiologically dominant. Our results are broadly in line with the literature(30).

Most cases of amyloidosis of the cervicofacial region are localized, AL-type and primary forms(31). For Jacques and al, expression of amyloidosis in the head and neck occurs in around 20% of cases(32),(33). In some cases, where amyloidosis is in its pseudotumor form , it may be proliferative , with massive lymph node infiltration, and thus mimicking a malignant process (34).In our series, we reported a case who presented a tumoral syndrome of the cavum with multiple rapidly progressive cervical lymph nodes, leading to suspicion of an indifferent undifferentiated carcinoma of the cavum.

Bone histiocytosis accounts for around 50% of localization in adults, particularly in the skull. Maxillary and mandibular involvement appears to be particularly frequent in adults (35). Whereas otorhinolaryngological disorders predominate in pediatrics(36). This topographical distribution in accordance with age is valid for our study. This features in 2 cases of histiocytosis, the first in a seven-year-old child with central diabetes insipidus related to a hypothalamic tumor associated with cervical lymph nodes and the second is 58 years old with an isolated mandibular involvement.

In pemphigus vulgaris, involvement of the ENT mucosa is often predominant, sometimes manifesting as mucosal erosion and/or erosive gingivitis. Skin involvement can occur simultaneously or may appear weeks to months later, as observed in our patient. It is characterized by the presence of transparent, non-itchy, flaccid blisters on otherwise healthy skin.(37)

The diagnosis of Castleman's disease is confirmed histologically, supported by a suggestive clinical and radiological presentation. In our case, histological confirmation was achieved only through surgical resection, as preoperative biopsies were non-diagnostic.(38)

Melkersson Rosenthal syndrome (MRS ) is an orofacial granulomatosis characterized by a symptomatic triad: a cracked tongue, macrocheilia due to labial edema and recurrent facial paralysis(39). Orofacial oedema is the cardinal sign of the syndrome and is sufficient to the diagnosis after eliminating other differential diagnoses. Our patient had a complete syndrome, even though the 3 symptoms appeared two years apart, which is rarely reported in the literature (40).

## CONCLUSION:

The localization of systemic diseases within the ENT sphere is uncommon characterized by clinical and etiological variability. In our study, ENT involvement appeared at the forefront of systemic disease in 31 cases (78%) and was revelatory in 13 cases (42%). It was discovered during the course of the disease in 22%cases, with a mean time to onset of 59 months [24-108 months]. Etiologies were dominated by sarcoidosis (25%) and Sjögren's syndrome (18%).

ENT manifestations of systemic diseases are often unspecific. Consequently, it is crucial for ENT physicians to always keep in mind systemic diseases when confronted with any ENT manifestation, especially those demonstrating atypical evolution or accompanied by extra-ENT symptoms. This underscores the vital need for collaboration and cooperation between ENT specialists and internists.

**Conflict of Interest disclosure:**

The authors declare that there are not conflicts of interest

## REFERENCES:

1. Moya-Plana A, Pouchot J, Laccourrey O, Bonfils P. Manifestations oto-rhino-laryngologiques des maladies systémiques.EMC Oto-rhino-laryngologie. Oct 2010. [20-958-A-10]. Doi: 10.1016/S0246-0351(12)58641-1 .
2. Knopf A, Bas M, Chaker A, Strassen U, Pickhard A, Stark T, et al. Rheumatic disorders affecting the head and neck: underestimated diseases. Rheumatology (Oxford). Nov 2011; 50(11):2029-34.
3. Iguelouane N, Skandour D, Rochdi Y, Nouri H, Aderdour L, Raji A. Les manifestations ORL dans les maladies systémiques: à propos d'une série de 200 cas. Annales Françaises d'Oto-Rhino-Laryngologie et de pathologie cervico-faciale. Oct 2014;131(4):A127. Doi: 10.1016/j.aforl.2014.07.27
4. Borgia F, Giuffrida R, Guarneri F, Cannavò SP. Relapsing Polychondritis: An Updated Review. Biomedicines. Aug 2018;2:6(3):84. DOI: 10.3390/biomedicines6030084
5. Kühn D, Hospowsky C, Both M, Hey M, Laudien M. Manifestation of granulomatosis with polyangiitis in head and neck. Clin Exp Rheumatol. 2018;36 Sup111(2):78-84.
6. Hinschberger A, Rousseau A. Le syndrome de Melkersson-Rosenthal: à propos de 16 cas . La Revue de médecine interne 32S (2011) S45–S98
7. Kwon YS, Jung HI, Kim HJ, Lee JW, Choi WI, Kim JY, et al. Isolated cervical lymph node sarcoidosis presenting in an asymptomatic neck mass: a case report. Tuberc Respir Dis (Seoul). sept 2013;75(3):116-9.
8. Butler CR, Nouraei SAR, Mace AD, Khalil S, Sandhu SK, Sandhu GS. Endoscopic airway management of laryngeal sarcoidosis. Arch Otolaryngol Head Neck Surg. mars 2010;136(3):251-5.
9. Salah S, Abad S, Brezin A, Monnet D. Sarcoidosis. Journal français d'ophtalmologie. 2018;41:e451–67. https://doi.org/10.1016/j.jfo.2018.10.002.
10. Arvind K Badhey 1, Sameep Kadakia, Ricardo L Carrau, Codrin Iacob, Azita Khorsandi , Sarcoidosis of the head and neck , Head Neck Pathology 2015 Jun;9(2):260-8.
11. Duchemann B, Lavolé A, Naccache JM, Nunes H, Benzakin S, Lefevre M, et al. Laryngeal sarcoidosis: a case-control study. Sarcoidosis Vasc Diffuse Lung Dis. 20 oct 2014;31(3):227-34.
12. Aubart FC, Ouayoun M, Brauner M, Attali P, Kambouchner M, Valeyre D, et al. Sinonasal involvement in sarcoidosis: a case-control study of 20 patients. Medicine (Baltimore). nov 2006;85(6):365-71.
13. Braun JJ, Riehm S, Imperiale A, Schultz-Carpentier AS, Gentine A, de Blay F. Sarcoïdose des voies aérodigestives supérieures. Revue des Maladies Respiratoires. 1 févr 2011; 28(2):164-73.
14. Gulati S, Krossnes B, Olofsson J, Danielsen A. Sinonasal involvement in sarcoidosis: a report of seven cases and review of literature. Eur Arch Otorhinolaryngol. mars 2012;269(3):891-6.

15. Aboudib F, Benzakour M, Moudatir M, Bouissar W, Alaoui FZ, et al. L'atteinte ORL dans la sarcoïdose: 17 cas. La Revue de Médecine Interne. Dec 2015;36:A174-5.
16. Soua M, Ameur K, Soua Y, Lahouel I, Youssef M, Zili J. Syndrome de Mikulicz révélateur d'une sarcoïdose. Annales de Dermatologie et de Vénéréologie. May 2018;145(4Sup). A80.
17. Retamozo S, Acar-Denizli N, Rasmussen A, Horváth IF, Baldini C, Priori R, et al. Systemic manifestations of primary Sjögren's syndrome out of the ESSDAI classification: prevalence and clinical relevance in a large international, multi-ethnic cohort of patients. Clin Exp Rheumatol. May-Jun 2019;37 Sup 118(3):97-106. Epub 2019 Aug 28. PMID: 31464664.
18. Bakshi J, Venables PJ, Abraham S. Sinonasal sarcoid. J Postgrad Med. 2009;55(1):43-4.
19. Arnaud L, Mathian A, Haroche J, Gorochov G, Amoura Z. Pathogenesis of relapsing polychondritis: a 2013 update. Autoimmun Rev. Fev 2014;13(2):90-5.
20. Puéchal X, Terrier B, Mouthon L, Costedoat-Chalumeau N, Guillevin L, Le Jeunne C. Polychondrite chronique atrophiante. Revue du Rhumatisme. Mai 2014;81(3):213-9.
21. Pakalniskis MG, Berg AD, Policeni BA, Gentry LR, Sato Y, Moritani T, et al. The Many Faces of Granulomatosis With Polyangiitis: A Review of the Head and Neck Imaging Manifestations. AJR Am J Roentgenol. déc 2015;205(6):W619-29.
22. Arslan S, Işik AÜ, Mungan S, Ural A, Sari RA. Wegener's granulomatosis with an atypical presentation as acute tonsillitis. ORL J Otorhinolaryngol Relat Spec. 2014;76(1):57-61.
23. Greco A, Marinelli C, Fusconi M, Macri GF, Gallo A, De Virgilio A, et al. Clinic manifestations in granulomatosis with polyangiitis. Int J Immunopathol Pharmacol. Juin 2016;29(2):151-9.
24. Alam DS, Seth R, Sindwani R, Woodson EA, Rajasekaran K. Upper airway manifestations of granulomatosis with polyangiitis. Cleve Clin J Med. nov 2012;79 Suppl 3:S16-21.
25. Hadj Said M, Foletti JM, Graillon N, Guyot L, Chossegros C. Orofacial manifestations of scleroderma. A literature review. Rev Stomatol Chir Maxillofac Chir Orale. nov 2016;117(5):322-6.
26. Baldwin C, Wolter NE, Pagnoux C. Ear, nose, and throat involvement in eosinophilic granulomatosis with polyangiitis. Advances in Cellular and Molecular Otolaryngology. 2015;3(1). https://doi.org/10.3402/acmo.v3.27181
27. Goldfarb JM, Rabinowitz MR, Basnyat S, Nyquist GG, Rosen MR. Head and Neck Manifestations of Eosinophilic Granulomatosis with Polyangiitis: A Systematic Review. Otolaryngol Head Neck Surg. Nov 2016;155(5):771-8.
28. Durel CA, Berthiller J, Caboni S, Jayne D, Ninet J, Hot A. Long-Term Followup of a Multicenter Cohort of 101 Patients With Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss). Arthritis Care Res. Mar 2016;68(3):374-87.
29. Mouthon L. Épidémiologie, classification des connectivites. JMV-Journal de Médecine Vasculaire. Mar 2018;43(2):74.
30. Coste A. Polypose nasosinusienne et médecine interne. La Revue de Médecine Interne. Juin 2011;32(1):5-8.
31. Huart C, Renaudin Autain K, Barbey C, Lescanne E, Malard O. ENT localisation of amyloidosis: 20 patients report. Rev Laryngol Otol Rhinol. 2015;136(3):103-7.
32. Jacques, C. Giddings, P. Hawkins , Head and neck manifestations of amyloidosis T A , The Otorhinolaryngologist 2013; 6(1):35-40.
33. Singh A, Haq M, Gautam P, Gautam D, Handa AC, Handa KK, et al. Clinical Profile of Patients with Head and Neck Amyloidosis: A Single-Institution Retrospective Chart Review. Int. Arch. Otorhinolaryngol. 2020;24(4):e450-e456
34. Güllü BE, Hatemı I, Ozbay G, Tüzüner N, Sonsuz A. A rare case of primary systemic amyloidosis presenting with hepatic failure. Turk J Gastroenterol. 1 févr 2011;22(1):113-4.
35. Néel A, Artifoni M, Donadieu J, Lorillon G, Hamidou M, Tazi A. Langerhans cell histiocytosis in adults. Rev Med Interne. Oct 2015;36(10):658-67.
36. Héritier S, Donadieu J. Histiocytose langerhansienne chez l'enfant. Perfectionnement en Pédiatrie. Sep 2021;4(3):248-56.
37. Ingold CJ, Sathe NC, Khan MAB. Pemphigus Vulgaris. 2024 Mar 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32809695.
38. Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. Blood. 2020 Apr 16;135(16):1353-64. Doi: 10.1182/blood.2019000931. PMID: 32106302.
39. Vignes S, Chaillet M, Cabane J, Piette JC. Perforation de la cloison nasale et maladies systémiques. La Revue de Médecine Interne. Nov 2002;23(11):919-26.
40. Dhawan SR, Saini AG, Singhi PD. Management Strategies of Melkersson-Rosenthal Syndrome: A Review. Int J Gen Med. 2020;13:61-5.