

Eosinophilic granulomatosis with polyangiitis and oral lesions: an atypical first sign of the disease. A literature review

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KEYWORDS Churg-Strauss syndrome; Oral ulcer; Vasculitis; Mouth diseases; Eosinophilic Granulomatosis with Polyangiitis.

ABSTRACT

Aim Eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss Syndrome) belongs to the group of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) together with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis). Ear, nose and throat (ENT) manifestations in AAV are relatively common and in some cases the first sign of the disease; in contrast, oral lesions are less frequent and described in only a very limited number of case reports of EGPA. Although not curable, AAV can be successfully managed with immunosuppressive drugs and other novel agents, highlighting the importance of early diagnosis.

Methods Herein, we reviewed the results of a literature search for descriptions of oral lesions in EGPA. A literature review was conducted, consisting of a literature search, pragmatic searches of web sources and snowballing.

Results The few cases reported document that oral lesions can occasionally be the first sign, albeit atypical, of the disease.

Conclusions Healthcare professionals who examine the oral cavity, and especially otolaryngologists and dentists, should always consider EGPA in the differential diagnosis of oral lesions to avoid delayed diagnosis and, most importantly, the potentially fatal consequences of the vasculitic stage of the disorder.

reported for the first time by Davies et al. in 1982 (2). AAV were originally described in 1954 by Godman and Churg who noticed three features: systemic necrotizing "angiitis," necrotizing inflammation of the respiratory tract, and necrotizing glomerulonephritis (3). In 2012, the International Chapel Hill Consensus Conference (CHCC) revised the AAV nomenclature by including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss Syndrome) in the group (4). Among other symptoms, ear, nose and throat (ENT) manifestations in AAV are common and in some cases the first sign of the disease (5). On the other hand, oral lesions are less frequent manifestations of AAV, and although described in GPA as strawberry gingivitis (6,7) they have been documented in only a very limited number of case reports in EGPA (8).

The objective of this review is to describe the intraoral ulcerations in EGPA reported in literature to date, in order to increase awareness on this extremely rare manifestation of the disease.

Search strategy

A literature review was conducted, consisting of a literature search, pragmatic searches of web sources, and "snowballing". Publications reporting data on EGPA and oral lesions were identified through MEDLINE. Search strategy combining the following concepts was developed using the following free-text keywords and MeSH headings: disease of interest ("Granulomatosis with Polyangiitis", "Churg Strauss", "antineutrophil cytoplasmic antibody associated vasculitis", "EGPA") and clinical manifestations of interest ("oral ulcer", "mouth diseases", "tongue diseases"). Pragmatic searches of the grey literature were conducted using Google and

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of small-vessel vasculitides with absent or limited vascular immune deposits (1), characterized by the presence of antibodies directed against the neutrophil cytoplasm (ANCA) that were

Google Scholar search engines. These searches aimed at identifying additional relevant sources not captured in the literature search because they were not indexed in electronic bibliographical databases or because they were indexed using different terms. The list of references of selected publications including reviews were screened for additional sources. Only publications in English were included. Given the specificity of the topic, no further restrictions were applied.

Eosinophilic granulomatosis with polyangiitis

Churg-Strauss syndrome was first described in 1951 (9) and more recently renamed EGPA, eosinophilic granulomatosis with polyangiitis (4). Like the other AAVs, EGPA is a systemic necrotizing vasculitis that affects small vessels in different organs. Churg and Strauss first noticed the following features of the syndrome: asthma, eosinophilia, fever, and involvement of different organs including heart and kidney damage (9). In 2012, CHCC highlighted the allergic component of EGPA: peripheral eosinophilia, asthma and eosinophil-rich and necrotizing granuloma of the respiratory tract (4). Although several definitions and classification criteria have been proposed for EGPA by different groups, definitive and validated diagnostic criteria are still not available (10). In chronological order, among the most used there are: the 1990 American College of Rheumatology (ACR) criteria, the 2007 European Medicine Agency (EMA) algorithm for the classification of AAV and polyarteritis nodosa, and finally the 2012 CHCC criteria (10).

EGPA has an incidence ranging between 0.6 and 6.8 per million population per year, and occurs more frequently in patients aged 40-60 years, with no clear gender preponderance (11). Three different clinical stages have been described: an initial or prodromic allergic stage characterized by asthma, sinusitis and allergic rhinitis; a second eosinophilic stage with peripheral eosinophilia and clinical manifestations of organ eosinophilic infiltration; and a final vasculitic stage with the most severe clinical features of necrotizing vasculitis (lung

involvement, skin manifestations, peripheral nervous system involvement, gastrointestinal manifestations, kidney involvement, heart involvement). The prodromic allergic phase can precede other symptoms by 5-10 years, and this makes the differential diagnosis with other allergic diseases quite complex (12). Other etiologies with head and neck midline granulomatous lesions to be considered include: tuberculosis, tertiary syphilis, GPA, sarcoidosis, cocaine-induced midline destructive lesions, NK T-cell lymphoma, and squamous cell carcinoma (13-22).

ANCA positivity in EGPA has been reported to range between 30% and 70% (23), with the majority of patients presenting with perinuclear ANCA specific for myeloperoxidase; additionally, laboratory tests show peripheral eosinophilia and high IgE levels. EGPA association with asthma and peripheral eosinophilia distinguishes it from GPA and MPA, but it is often confused with parasitic infections and hypereosinophilic syndromes, especially in patients who are ANCA negative (24).

Ear, nose and throat manifestations and oral lesions in eosinophilic granulomatosis with polyangiitis

EGPA related ENT involvement is relatively common both in the prodromic allergic and eosinophilic stages. While allergic rhinitis and chronic rhinosinusitis with or without polyps are commonly described in EGPA, granulomatous destructive lesions, such as septal perforation or nasal framework collapse, are more typical of GPA and can be helpful in making a correct differential diagnosis (5). Other ENT manifestations may include: crusting rhinitis, otitis media with effusion, chronic suppurative otitis media, vestibular impairment, sensorineural hearing loss with tinnitus, and dizziness (25,26). In the literature, ENT symptoms in EGPA patients are reported to range from 48% to 77% (27-31). Among other studies, three cohorts of EGPA patients have been reported in recent years: 118 patients treated in France, Belgium, and UK described by Samson et al. in 2013 (32), 383 patients enrolled in



FIG. 1 Shallow ulcers in the lower labial vestibulum with pattern similar to herpetiform aphthous stomatitis.



FIG. 2 A milder case of labial lesions.

AUTHOR	YEAR	TYPE OF PUBLICATION	COUNTRY	ORAL LESION DESCRIBED
DEL PLACE	2007	Case report	Belgium	Palatine ulcerations
BALDINI	2014	EULAR* abstract	Italy	Mouth ulcers
IVANOFF	2018	Case report	USA	Oral ulcerations
OTSUKA	2019	Letter to Editor	Japan	Oral ulcers

TABLE 1 List of published literature on EGPA and oral lesions (EULAR: European League Against Rheumatism).

the French Vasculitis Study Group Cohort published by Comarmond et al. in 2013 (31), and 315 patients from a cross-sectional nationwide survey performed in Japan included in Sada et al. in 2014 (33). All three studies report ENT involvement in EGPA patients: in particular, Samson described ENT symptoms in 75% of patients (crusting 9%, sinusitis 68%, otitis 5%), Comarmond in 48% of patients (rhinitis 17%, sinusitis/polyposis 41.8%), and Sada in 23% of the Japanese patients, although the author comments that some mild nasal and paranasal sinus disease might not have been included in the survey from which data was gathered.

Although not typical, oral manifestations have been described in GPA (34). In particular, gingival inflammatory and necrotizing lesions, also defined as "strawberry gingivitis", might be one of the earliest manifestations of GPA and also highly suggestive of the disease from a clinical and histopathological point of view (6). In contrast, Delplace et al. (35) published the first case report in 2007 describing an oral ulceration in a patient with EGPA (Table 1). The authors observed painful palatine ulcerations in a 15-year-old female patient with EGPA (35), which appeared a week earlier than the facial and hand lesions. The palatine ulceration was well-demarcated with a necrotic base and an erythematous halo around it. Several other small oral ulcerations similar to common aphthous lesions were also described. In the patient's medical history, chronic sinusitis, nasal polyposis, and allergic asthma were reported. A diagnosis of EGPA was finally made when laboratory tests revealed eosinophilia (31.7%) and high IgE (1701 UI).

Baldini et al., in 2014 (36) described 53 EGPA patients in a single-center observational study with the objective to assess the damage accrued by patients during the course of the disease using the Vasculitis Damage Index. Damage manifestations were listed by presumed etiology: secondary to EGPA, to therapy, or both. Among those items of damage potentially related to both treatment and disease activity, 1.9% of mouth ulcers were listed, implying oral lesions are part of the accrued damage in EGPA (36).

A further case of oral ulcerations in a 64-year-old woman with EGPA was reported by Ivanoff et al. in 2018 (8). The case was of particular interest because the oral lesions on the tongue, labial mucosa and floor of the

mouth appeared about six months before renal disease (which presented as crescentic glomerulonephritis). Painful oral ulcerations presented with features similar to minor aphthae on non-keratinized oral mucosa, or major aphthae, that were larger and deeper, on the sides of the tongue and floor of the mouth, and very small herpetiform aphthae on the tip of the tongue. Biopsy revealed that the ulcerations were not specific and non-neoplastic. Although the patient complained of difficult and painful speaking and eating, the ulcers healed spontaneously after each of the three outbreaks. Only during a subsequent admission to the hospital due to the onset of systemic symptoms was a diagnosis of EGPA finally made. The authors highlighted how oral ulcerations preceded every other symptom in the diagnosis of EGPA, and that it is pivotal to consider AAV in the differential diagnosis of intra-oral lesions (8). In 2019, an additional case of oral lesions in a patient diagnosed with EGPA was reported by Otsuka et al. (37). A 49-year-old woman presented with painful oral ulcers with necrotic tissue on the gingiva, palate, tongue, and floor of the mouth that had been present for several months. Palpable purpura was present on the face and the scalp, together with papules and subcutaneous nodules on the limbs. The patient's medical history revealed bronchial asthma, which had appeared one year earlier, and sudden deafness from three years earlier. Diagnosis of EGPA was confirmed according to ACR criteria when a biopsy from the tongue showed eosinophil infiltration and computed tomography demonstrated bronchial wall thickening and centrilobular patchy opacities.

CONCLUSIONS

EGPA is a rare disease belonging to the group of AAV for which definitive diagnostic criteria are not available (10). The updated 2012 CHCC definition reads: "EGPA is eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia" (4). Although not curable, EGPA can be successfully managed with immunosuppressive drugs and other novel agents (10). Therefore, early detection is essential to avoid the potentially fatal

consequences of the vasculitic stage of the disorder (8). Allergic rhinitis, sinusitis, and asthma are the most common clinical features of the prodromal stage, which make differential diagnosis extremely complex (38–40). In most cases, diagnosis is delayed until the more pathognomonic manifestations present, such as blood or tissue eosinophilia, ANCA positivity, or late stage organ damage due to necrotizing vasculitis (10). Considering ENT symptoms are present in about 48%–77% of cases (27–31), the otolaryngologist plays an essential role in the multidisciplinary team (25–41). Besides the more common ENT manifestations, in rare cases oral lesions have been reported as the first indicator of the disease, which must alert otolaryngologists, dentists, and other healthcare professionals who examine the oral cavity. Unfortunately, oral lesions described to date in EGPA are not specific and very common in many other systemic or local diseases, representing a significant problem in terms of differential diagnosis. The latter might delay diagnosis in the later stages of the disorder when management becomes more complicated. Physicians should always consider EGPA as a potential diagnosis when oral lesions are associated with asthma (mostly late onset asthma), allergic rhinitis, and eosinophilia, especially in middle-aged patients. Furthermore, in such cases monitoring blood cell counts, including eosinophils, is highly recommended (8). In conclusion, this review of the few cases reported in literature of EGPA associated with oral lesions suggests that such rare manifestation can be the atypical first sign of the disease, even if infrequently.

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Conflict of Interest

None of the authors have any conflict of interest.

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