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Oral lesions in Granulomatosis with polyangiitis (GPA): An updated overview

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ABSTRACT

Aims Granulomatosis with polyangiitis (GPA) is one of the three primary systemic autoimmune vasculitis associated with anti-neutrophil cytoplasmic antibodies. In particular, GPA is characterized by inflammation of small and medium-sized blood vessels that may affect different organs, such as kidneys, lungs and, most commonly, upper respiratory tract. Lesions of the oral cavity, are represented by a group of non-specific lesions that include deep ulcers of tongue, cheek and palate with the presence of oro-antral fistulae, osteonecrosis of hard palate and labial mucosal nodules. However, the most pathognomonic GPA oral lesion is the so called "strawberry" gingival hyperplasia, a gingival swelling of reddish colour with scattered darker petechiae. Generally, such lesions are present in about 6-13 % of GPA patients; however, the recognition of oral lesions can help in establishing early diagnosis and treat the disease avoiding severe systemic involvement.

Methods A literature review consisting of a thorough literature search was performed. Granulomatosis with polyangiitis (GPA) and oral lesions publications were selected from PubMed/ Medline. The following keywords and MeSH headings were used for the search strategy: Granulomatosis with Polyangiitis, Wegener granulomatosis, antineutrophil cytoplasmic antibody associated vasculitis, mouth lesions, and strawberry gingivitis.

Results Clinical and radiological features are important tools in early diagnosis, but mucosal biopsies of the upper respiratory tract are still the "gold standard" of GPA. Proper diagnosis is mandatory in order to successfully treat the pathology.

Conclusions These findings underscore the importance of performing a complete oral examination, along with complete anamnesis and clinical evaluation, in all patients in whom GPA is suspected.

INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a systemic autoimmune vasculitis associated with anti-neutrophil cytoplasmic antibodies (c-ANCA) directed against proteinase-3 (PR3) that involves small and medium sized arteries. The antibodies involved usually generate an uncontrolled reaction characterized by neutrophils activation, followed by recruitment of other inflammatory cells, with particular involvement of T-helper lymphocytes. Such immunological activation results in an inflammatory infiltration of small and medium-sized blood vessels, leading to a multi-organs damage involving the kidneys, lungs, mucous membranes and skin (1). However, even if the pathological mechanism is well defined, GPA has a complex and unclear pathogenesis, with a possible role of infectious, environmental and genetic factors with an incidence that varies between 2–12 per million per year in general population, and is more common in Caucasians than in other ethnic groups (2).

Diagnosis of GPA is based on American College of Rheumatology Criteria, which require at least two of the following features: 1) nasal discharge or oral ulcers, 2) nodules, cavities or fixed infiltrates on a chest radiograph, 3) abnormal urinary sediment (microscopic haematuria with or without red cell casts) and 4) granulomatous inflammation on biopsy of an artery or perivascular area (3). However, in clinical practice, the presence of distinctive ANCA antibodies and a positive biopsy of any affected organ play a major role (4). Nevertheless, due to nonspecific symptoms in the early stage, diagnosis is often delayed and is steadily fatal without adequate treatment (2).

GPA can be present both in the young and elderly, but the age at the diagnosis is generally 45-65 years without

important differences between men and women (2).
Moreover, childhood-onset of ANCA associated vasculitides (AAV) is quite rare comparing to adult population and data coming from cohort studies are heterogeneous and scarce; unlike adult population, there is a high female predominance of childhood GPA, with a median age at diagnosis of approximately 12–14 years (5,6). Clinical features of GPA in children are similar to those of adult, presenting either as an acute small vessel vasculitis associated with progressive renal impairment and lungs haemorrhage or as localized granulomatous disease with a chronic evolution (6). The most common feature in childhood GPA is represented by upper respiratory tract involvement with symptoms like sinusitis, epistaxis, otitis media and hearing loss (6). However childhood-onset GPA is associated with frequent relapses, higher prevalence of nasal deformities, such as saddle nose, and renal involvement at presentation than adulthood GPA form; it must be also noted that subglottic stenosis is a life-threatening condition that has been registered at presentation in 10 to 20% and results more common in pediatric if compared to adults cohort (5,7). Because of the rare nature of the disease, childhood-onset GPA treatment is often extrapolated from adult therapy and early diagnosis and treatment play a crucial role in the long therm outcome of pediatric AAV (5,7).
GPA can be classified as early systemic, localized or generalized phenotype, which classically present involvement of the ELK triad characterized by ear, nose, throat (E), lungs (L) and kidneys (K) with vasculitis and necrotizing granulomatous inflammation (2,8). According to European Vasculitis Study Group (EUVAS) disease categorization for GPA disease severity is assessed as following: localized form of ANCA associated vasculitis (AAV) is characterized by ear, nose and throat (ENT) or pulmonary involvement with serum creatinine levels < 120 µmol/l (1.3 mg/dl); early systemic disease is defined by both ENT and pulmonary manifestations with involvement of an organ outside the upper respiratory tract and serum creatinine levels < 120 µmol/l (1.3 mg/dl) without life-threatening disease; generalized form is defined as vasculitis in organs outside the ENT and lungs, threatened function of vital organ and serum creatinine levels < 500 µmol/l (5.5 mg/dl); severe form includes cases with vasculitis in organs outside the ENT and lungs, failure of vital organ function and serum creatinine levels > 500 µmol/l (5.5 mg/dl); finally it must be considered a refractory form when characterized by progressive disease unresponsive to cyclophosphamide and glucocorticoids therapy (9,10).
Moreover, even if the most common symptom is sinusitis, occurring in 73% of patients, middle ear involvement, with serous otitis and hearing loss, may be the presenting phenomenon in 25% of patients (11,12). ENT involvement (sinuses, ears, oral cavity and throat) are thought to be the first manifestation of the disease in 80-95% of patients, while oral cavity pathologies usually present late in the disease (11,13,14); additionally, it needs to be noted that otorhinolaryngological symptoms are often the only sign of localized GPA, a specific form in which ANCA may not be present, which is more frequent in young females and is more recurrent and refractory in comparison with the generalized form (4,15).
Antineutrophilic cytoplasmic antibodies (ANCA) directed against myeloperoxidase (MPO) or proteinase 3 (PR3) are sensitive and specific markers for small vessel vasculitis such as GPA (16-20). In particular, c-ANCA directed against proteinase-3 (PR3) has predominantly been associated with GPA, while p-ANCA, directed against myeloperoxidase antigen (MPO) has been more frequently associated with microscopic polyangiitis (MPA) and other forms of vasculitis (11).
Differential diagnosis between GPA and microscopic polyangiitis (MPA) can be demanding because of significant overlap in the signs and symptoms and in the ANCA sierologies. In fact, patients initially presenting with only symptoms consistent with MPA, could later develop manifestations more compatible with GPA (10). The difficulty in reaching a correct diagnosis have a clinical rebound, since different therapies may be required for some lesions, such as upper respiratory tract disease and since the rate of relapse is different in MPA and GPA (9,21). As previously stated, GPA often presents with clinical involvement of organs forming a "classic triad" which includes ENT and lower respiratory tract affection (in particular pneumonia and haemoptysis) with coexisting renal disorders; MPA presents similar pulmonary involvement and renal disfunction, while ENT involvement is much more rare than in GPA disease (10). In particular, ENT symptoms in the early clinical picture reach 56.52% in MPA and 85.37% in GPA according to a recent cohort study (10). According to several studies, the most common disease manifestation in the head and neck area in both GPA and MPA, is chronic rhinosinusitis with subsequent epistaxis and purulent nasal discharge; in both groups, ears are often affected by chronic otitis media and sensorineural hearing loss while oral cavity may be interested by peculiar gingival hyperplasia with dark scattered petechia, without differentiating microscopic features at biopsy specimen (10,22-24). It must be noticed that localized disease is more common in GPA than in MPA, but MPA predispose to severe evolution of systemic disease more frequently than GPA. (10,25). Both in GPA and MPA, complete blood count (CBC) usually reveal leukocytosis with neutrophilia, lymphopenia and anaemia, while urinalysis show microscopic haematuria or gross haematuria and proteinuria in most cases. Increased serum creatinine and urea levels, ESR and CRP are also often observed in both small vessel vasculitides (10). Therefore, even if GPA patients are more prone to present ENT disorders than those with MPA, head and neck involvement is a common early presentation both in GPA and MPA, preceding systemic, life-threatening organ disorders. This evidence highlights the crucial role of ENT

complete evaluation in early diagnosis and management of ANCA associated vasculitides (10,24). Some authors suggest that Staphilococcus Aureus (S. Aureus) may work as a molecular mimicry for proteinase 3 (PR3) and may act as a trigger of PR3-ANCA autoantibody production (10). Moreover it has been noticed that patients with GPA with nasal carriage of S. Aureus usually presents with localized disease and are more predisposed to disease relapses, during remission period; this could explain the efficacy of anti-staphylococcal prophylaxis with trimethoprim/sulfamethoxazole in patients with remission (5,10). However it remains still uncertain if S. Aureus plays a pathogenetic role in GPA disease and other small vessel vasculitides, such as MPA (10).

In generalized GPA, ANCA are increased in 90-95% of patients, in localized phenotype, involving the ear nose and throat region, while positive levels of ANCA may occur in only 46-70% of patients, so that, making a correct diagnosis often requires a biopsy in the localized form (4). On the other hand, many disorders in differential diagnosis with GPA, including malignancies such as Hodgkin's lymphoma, connective tissue disorders, monoclonal gammapathies, nasal septal perforation and infection (tuberculosis, human immunodeficiency virus infection) present false positive c-ANCA test results (11,26). Therefore, c-ANCA may not be useful in diagnosis in cases of limited or early disease by itself, because of its positivity in many disorders in differential diagnosis with GPA (27). In addition, it should be noted that localized GPA may be in differential diagnosis with many diseases involving the upper respiratory tract, including infections (bacteria, fungus, mycobacteria, spirochetes), neoplasms and other inflammatory conditions (Churg Strauss syndrome, sarcoidosis, cocaine induced midline destructive lesions) (8,28-36).

This review aims to describe the oral lesions associated with GPA, discussing their clinical features and differential diagnosis, in order to raise awareness of this rare manifestation of the disease.

METHODS

A literature review was performed, consisting of a comprehensive literature search. Granulomatosis with polyangiitis (GPA) and oral lesions publications were selected from PubMed/Medline. The following keywords and MeSH headings were used for the search strategy: disease of interest ("Granulomatosis with Polyangiitis", "Wegener granulomatosis", "antineutrophil cytoplasmic antibody associated vasculitis") and clinical manifestation of interest ("mouth lesions", "strawberry gingivitis"). Only publications in English were selected. Given the specificity of the topic, no further restrictions have been applied.

RESULTS

Oral lesions of GPA are present in 6-13% of patients with GPA and are described as the first manifestation of the pathology in 5-6% of cases.

Oral manifestations of GPA are represented by lesions of various types, such as deep ulcers of the tongue, palate and cheek, ulcerations of the floor of the mouth, pharynx and tonsils.

The most typical lesion of GPA is the so-called "strawberry" gingivitis, a reddish-colored gingival hyperplasia associated with scattered petechiae.

The sometimes controversial clinical and radiological features of GPA are an important tool in obtaining an early diagnosis. However, mucosal biopsy of the upper respiratory tract still represents the diagnostic "gold standard" of the pathology.

Once the diagnosis of GPA is confirmed, a remission-induction and remission-maintenance therapy should be initiated. The therapeutic choice depends on the severity of the pathology and the presence of localized lesions or systemic pathology.

DISCUSSION

GPA is a systemic autoimmune vasculitis with involvement of different organs that can lead, if not properly treated, to multisystemic failure. GPA-related oral lesions are a group of possible organ pathologies that are often overlooked due to the unspecific clinical presentation that should be always considered in the diagnostic process.

Given the importance of effective recognition of GPA-related oral lesion, which may lead to early diagnosis, preventing secondary systemic involvement with poor prognosis, we propose this updated overview of GPA-related oral lesions, discussing their incidence, clinical features, differential diagnosis and role of the diagnostic process.

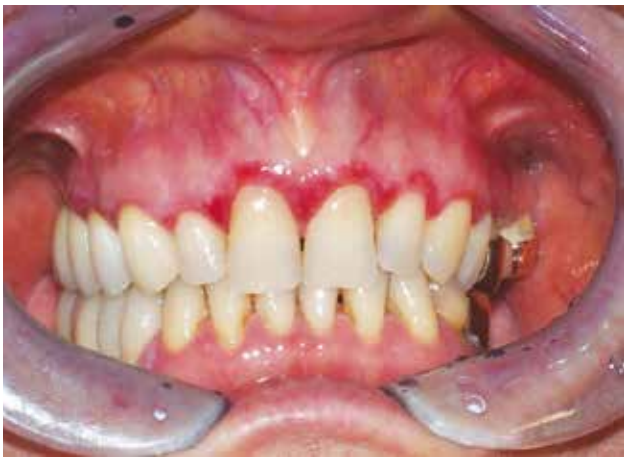
GPA oral lesions are usually present in about 6-13% of GPA patients and have been described as the initial manifestation in 5-6% of cases. The oral involvement may be observed many years before a generalized form occurs as well as in the advanced stages (2,8,15). Oral manifestations can be represented by a variety of lesions such as deep ulcers of tongue, cheek and palate, ulceration in the floor of the mouth, posterior pharynx and tonsils, as well as oro-antral fistulae, osteonecrosis of the hard palate and alveolar ridges and labial mucosal nodules (2,15,26,32). However, the most characteristic GPA-related oral lesion is the so called "strawberry" gingival hyperplasia, a gingival swelling of reddish to purple colour, friable, which can eventually extend to the palatal and lingual mucosa (2,15). Because of the periodontal involvement, osteomyelitis or necrosis of the underlying alveolar bone can develop with consequent abnormal mobility and loss of teeth (33,37). The term "Strawberry" gingival hyperplasia defines the reddish

colour of the lesion and the presence of darker petechiae; it originates from the interdental papillae and is a pathognomonic sign lesion, playing an important role in early diagnosis and treatment of GPA (15,24,34,38,39). In addition, some authors have described hyperplastic gingivitis as the first sign of recurrence of GPA in the absence of oral manifestations in the primary disease (40). Oral lesions of microscopic polyangiitis (MPA) nearly resemble strawberry gingivitis of GPA and are challenging to differentiate even by microscopy because of the lack of specificity in oral biopsy specimens. In fact, there are no differentiating microscopic features evident in oral lesions, so that diagnosis is often based on the results of ANCA testing (24,41). However, since the American College of Reumathology does not recognize a diagnosis of microscopic polyangiitis, such patients are usually classified as being affected by GPA, Henoch-Schonlein purpura and hypersensitivity angiitis (11,42). Due to the similarity of orofacial granulomatous lesions, differential diagnosis of mucosal ulcers should include systemic disease such as sarcoidosis, intestinal bowel disease (IBD), Melkersson-Rosenthal syndrome (MRS), and drug abuse or mycobacterial infections (2). However, while skin lesions of sarcoidosis usually vanish spontaneously in 2-4 week, granulomatous lesions associated with GPA persist for long periods if untreated (2). In addition, GPA is not usually associated with abdominal symptoms such as abdominal pain, diarrhoea and rectal bleeding, commonly associated with IBD, and does not present with recurrent facial paralysis or swelling of the face like in MRS (2). Gingival enlargement can be caused by medications, such as phenytoin, cyclosporine and some oral contraceptives, but if gingival hyperplasia is not associated with remission after periodontal therapy or with drug delivery, it should be investigated with regards to internal diseases like GPA or leukemia (31,33,35,37).Because of the crucial role of early diagnosis and treatment in GPA, those diseases should be quickly ruled out. In figures 1 to 6 we present some examples of oral lesions associated with GPA: all pictures are taken from patients with granulomatosis with polyangiitis.

As previously stated, cocaine abuse is another condition that can be considered in the differential diagnosis: in fact, cocaine abuse can cause massive destruction of the osseocartilaginous structures of the palate, nose and other midfacial structures, mimicking the clinical features of GPA lesions; downward progression of nasal destructive lesions of CIMDL, such as osteonecrosis of the hard palate and oro-antral fistula should not be confused with localized oral ulcerative lesions of GPA (15). However, comparing the clinical and radiographic findings in GPA patients with those of cocaine abusers, it is possible to detect different degrees and localizations of inflammatory changes: in fact, cocaine-induced midfacial destruction may involve nasal septum, inferior to middle turbinates, lateral nasal wall and nasal floor, while the inflammatory and necrotising lesions of GPA are usually less massive and more often limited to nasal septum (40,43). Palate perforation has been described in only five reports of subjects affected by GPA, while it is a common finding in cocaine abusers (44-46): as a consequence, this epidemiological difference is an important diagnostic element in differential diagnosis with GPA, especially when matched with negative biopsy and negative ANCA tests (44,46). Nevertheless, imaging studies with MRI show non-specific mucosal changes of the paranasal sinuses in both GPA patients and drug abusers, but also two different MRI signal patterns: in those with CIMDL, signal anomalies are more often localized to medial structures (nasal septum and turbinates), while in GPA patients the lesions are more scattered, reflecting widespread inflammation. These clinical and radiological differences could become a useful tool in differential diagnosis between those two diseases (47-52). Some cases of midline nasal and palatal erosions have been described in association with a novel systemic fibroinflammatory condition associated with IgG4 plasma cell, storiform fibrosis and obliterative phlebitis, thereby introducing an additional differential diagnosis to GPA and CIMDL. However, the incidence of IgG4-related disease (IgG4-RD) is still unknown and the disease presents specific histological hallmarks (40,43).

ANCA are a characteristic feature of GPA disease. However, as found by Trimarchi et al., patients who present with severe midfacial lesions associated with cocaine abuse may have a high frequency of positive ANCA tests (53). Therefore, routine ANCA tests does not frankly differentiate GPA from CIMDL and cannot be considered as valid diagnostic markers on their own. Wiesner et al. carried out a detailed analysis of ANCAs in GPA limited to upper respiratory tract and CIMDL and found a high frequency (84%) of anti-human neutrophil elastase (HNE) ANCAs only in patients with CIMDL (47,54). According to this finding, HNE ANCAs can be considered discriminatory, supporting a diagnosis of CIMDL in a clinical setting of necrotising inflammation of the upper respiratory tract; additional testing for HNE ANCAs could be useful in differential diagnosis, even if this diagnostic method is not commonly available in routine practice (49,54). Given these challenging differences, especially in localized GPA, the diagnostic "gold standard" is based on mucosal biopsies of the upper respiratory tract. However, even if vascular changes like chronic perivenulitis, micro abscesses and leukocytoclastic vasculitis have been proposed as specific hallmarks of GPA disease, similar lesions have been found in a large portion of biopsies from patients with CIMDL (45,46,50,53). Therefore, these histopathological features alone are of low sensitivity and specificity for GPA and are not useful in differential diagnosis. However, Trimarchi et al. noticed that extravascular changes such as extravascular foci of microscopic necrosis, scattered multinucleated giant cells and granulomas were found in a large number of GPA cases, but not in any of the biopsies obtained from

cocaine abusers (41,55). Therefore a definitive differential diagnosis between GPA and CIMDL is possible on the basis of extravascular changes on mucosal biopsies from the upper respiratory tract, highlighting the important rule of these features in the diagnosis of GPA (44,45,51,53,56).
Once the diagnosis of GPA is made, a two-stage treatment strategy, with remission-induction and remission-maintenance therapy, should be started (52). The choice of therapeutic agents depends on the severity of the disease and whether the lesions are generalized or localized (2,48,52). Induction therapy in severe generalized GPA requires cytotoxic therapy with cyclophosphamide and



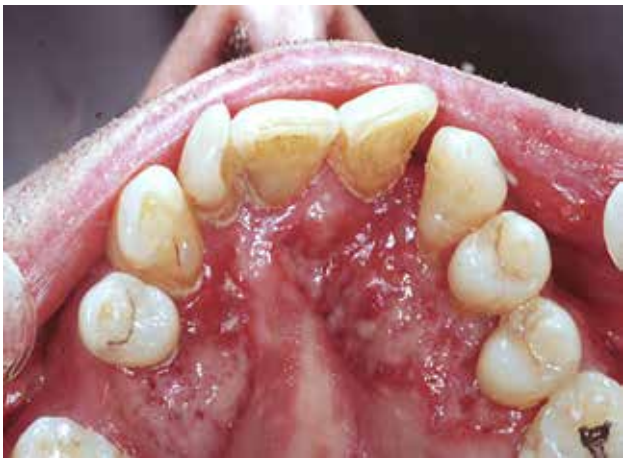
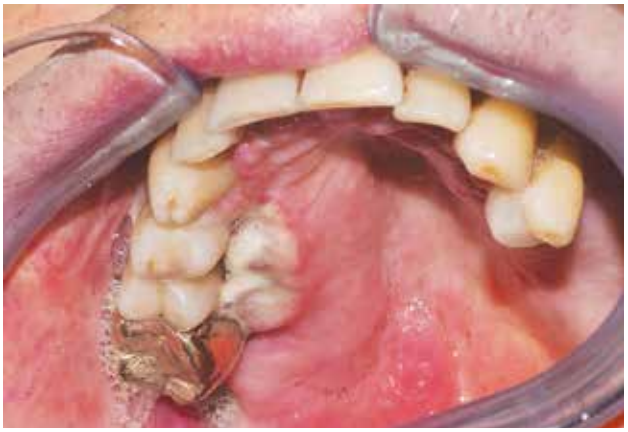


FIG. 1 Early stage of strawberry hyperplasia of upper marginal gingiva in GPA patient. FIG. 2 Strawberry gingivitis with a central necrotic area in the upper palatal gingiva in GPA patient.



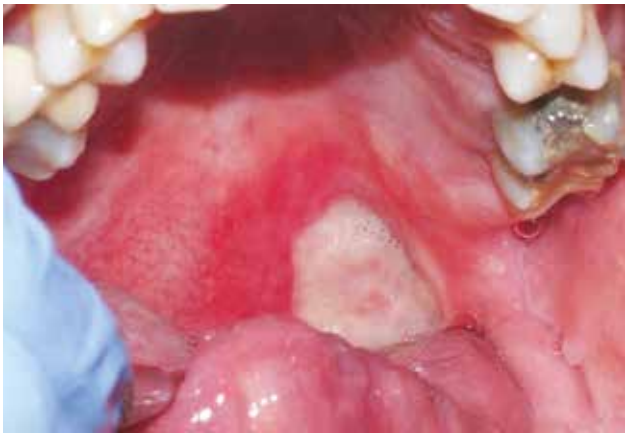
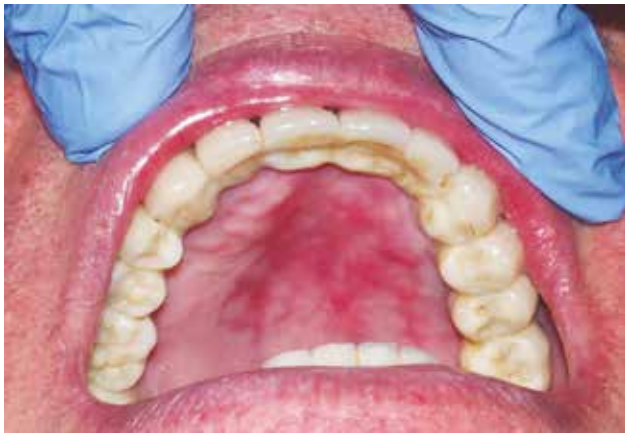


FIG. 3 Granulomatous ulcerative lesions of palatal gingiva in GPA patient. FIG. 4 Granulomatous ulcerative lesions of soft palate in GPA patient.



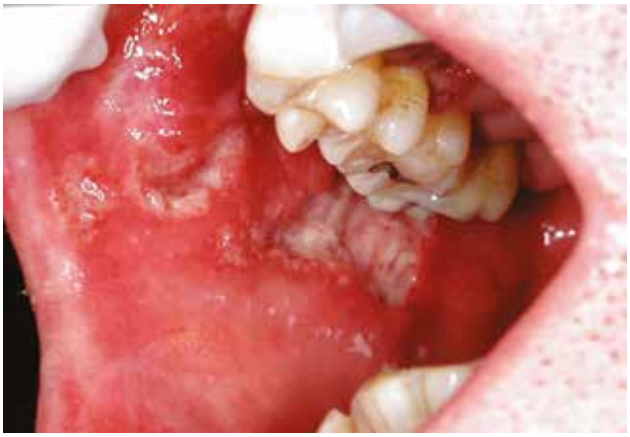


FIG. 5 Area of erythema of hard palate contiguous to a sinusal ulcerative lesion. FIG. 6 A multiple deep painful ulcers in the right buccal mucosa.
All pictures are by professor Silvio Abati.

high doses of glucocorticoids, while the combination of methotrexate and glucocorticoids are effectively used to induce remission in most patients with localized GPA (48,52,57,58). Oral lesions usually have a good response, with only occasional relapses, if appropriately treated (11). Once remission has been induced, remission maintenance can be achieved with a less toxic therapy, based on methotrexate and azathioprine, in both generalized and localized GPA disease (52). However, long term therapy with cyclophosphamide has been associated with severe side effects such as lymphoma, bone marrow suppression, haemorrhagic cystitis and bladder cancer (59,60). Therefore, the search of more tolerable alternative to cyclophosphamide and high-dose glucocorticoids is essential; rituximab, a chimeric monoclonal antibody directed against CD20 (antigen restricted to B cell precursor) could be a reasonable candidate. The latter agent, recently employed in autoimmune meningitis by intrathecal administration, has been shown to induce sustained and safe remission, when combined with glucocorticoids in GPA patients, as reported by a recent cohort study (49,54,61).

CONCLUSIONS

Oral lesions of GPA have been considered from the American Academy of Rheumatology a distinctive diagnostic criteria for GPA, underling their utmost importance for early stage diagnosis (8). Therefore, recognition of often overlooked oral lesions can help in establishing an early diagnosis, thus avoiding secondary serious systemic involvement. These findings underscore the importance of performing complete oral examination, along with a complete anamnesis and clinical evaluation, in all patients in whom GPA is suspected (27).

Conflict of Interest

None of the authors have any conflict of interest.

Authors' Contributions

All authors contributed to the conceptualization and writing of the article. All authors read and agreed to the published version of the manuscript.

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