Bullous disease after dental implant placement procedure: a case report highlighting clinical aspects

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Abstract:
IgA bullous dermatosis (LIgAD) is an uncommon diagnosis in Oral Medicine. The LIgAD-associated oral mucosa involvement was previously described by other authors and the clinical presentation is similar to other bullous diseases such as Pemphigus Vulgaris or other subtypes of Pemphigoids. The aim of this work is to report a case of a 63-years-old male who consulted for several painfully bullous lesions related to a story of non-treated cutaneous and ocular lesions. The patient referred the begin of the disease after a dental implant surgery procedure. The Direct Immunofluorescence allowed to show an IgA deposit in a linear pattern throughout the base membrane zone. After diagnosis, a corticosteroid treatment was applied with a huge improvement and healing of the lesions. This is the first case described in current literature of a rare bullous entity associated with a dental implant placement procedure. Since there was described several trigger factors related to dental practice, there should be more reports of these cases highlighting clinical presentation, therapeutic management and probable trigger factors for this entity.

Keywords: Linear IgA Bullous Dermatosis; Skin Diseases, Vesiculobullous; Dental Implants; Risk Factors

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INTRODUCTION

Ig A bullous dermatosis (LlGAD) is a bullous disorder described in 1979 by Jablonska and Chorzelski. The deposit of  IgA in a linear pattern in the basement membrane was a distinctive histopathological finding that makes LlGAD a different entity from the others bullous diseases1,4.

The LlGAD is a rare chronic autoimmune disorder, which clinically presents with the presence of blister on the skin and mucous membranes. Although first publications referred the onset of the disease in childhood, it can occur frequently in adults2. Recent published case-reports have previously shown the oral mucosa involvement, and the differential diagnosis between other bullous diseases such as Pemphigus Vulgaris and Pemphigoids3-6. LlGAD-related oral lesions can develop up to five years before skin involvement7, although in many cases the clinical presentation could be limited to the oral mucosa6.

The deposition of linear Ig A in the epithelium-chorion interface observable by direct immunofluorescence (DIF) techniques is the most useful tool to make the definitive diagnosis of this entity8,9. Although its idiopathic etiology10, there have been identified different triggering factors, such as drugs11,12.

The aim of this work is to present a clinical case of LlGAD, highlighting triggering factors, clinical presentation, as well as the management and treatment of the case. In addition, it is important to consider that, there was not been previously described a dental implant placement surgery as the possible trigger of this mucocutaneous disease.

CASE REPORT

A 63-years-old adult male attended to the Oral Cancer Early Detection Campaign performed in the Oral Medicine Department, Dentistry Colleague, Universidad Nacional de Córdoba in 2016. The chief complaint was a generalized burning mouth sensation. During the anamnesis, the patient reported long-standing mucocutaneous lesions. During the anamnesis, the patient referred the first lesions after dental implant surgery procedure. The cutaneous lesions were diagnosed and treated as non-specific-dermatitis with local drugs, with partial remission. 8 months after the appearance of the cutaneous lesions, he referred recurrent painful lesions which involved the palate area. In relation to systemic conditions, the anamnesis revealed hypertension, three coronary by-pass and moderate tobacco consumption.

During extraoral examination, different maculopapular lesions and scabs were found in the frontal region and scalp. The conjunctival mucosa was intensely erythematous with a foreign body sensation. Additionally, a synechia was observed in the lower left eyelid fixed to the eyeball (Figure 1 A-B-C). The oral examination showed multiple bullous lesions predominantly located on the hard palate, soft palate, buccal mucosa, floor of the mouth, gingival mucosa and vermilion border. The most important lesion was in the hard and soft palate area. It was evidenced a greyish pseudomembrane like an epithelial slough (bullous ceiling), with an erosive and erythematous surface with bleed tendency. The ceiling of the blister was firm, and it could be easily taken with a cotton tweezer (Figure 2 A-B).

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The other oral lesions were similar to those located in the palate, showing a generalized erythema. There were multiple haematic-crust-lesions located at the vermilion border (Figure 3A-B-C-D). The dental and periodontal exam showed a dental implant located in the anterior maxilla associated with a bone collapse. Intense fetid halitosis, poor oral hygiene with an advanced periodontal disease were also recorded. The clinical features led us to a provisional diagnosis of a Cicatricial Pemphigoid. The differential diagnosis with Pemphigus Vulgaris was also suggested. Routine haematological laboratories were requested. In order to decrease fungal and microbial colonization of erosive lesions, a local antifungal (Nystatin) and antibacterial (Chlorhexidine) prior to the diagnosis biopsy were prescribed.
Figure 2. A) Multiple bullae with and extended erythema throughout the palatine area were observed during intraoral examination. B) The firmed covered-epithelium of the bullae could be softly detached with a cotton tweezer. The exposed chorion showed inflammation with tendency to bleed.

Figure 3. A) Haematic crusts along the vermilion border. B) Buccal mucosa showed an extended erythema with conserved bullous lesions. C) The soft palate was completely involved by painful blisters and erosions which hindered swallowing. D) A greyish blister was found on the floor of the mouth. It could be also observed poor periodontal conditions.

One week later, the clinical appearance showed an important improvement, being more manifest the presence of bullous lesions free of oral microflora over-aggregated inflammation (Figure 4–A). An incisional biopsy was performed in a novel bulla created with a rubber bulb (Figure 4 B–C–D–E). The tissue was fixed in 10% formaldehyde. For DIF technique, healthy mucosal tissue adjacent to the injured tissue was obtained. The specimen for DIF was put in cold saline frozen before processing.

The haematological study showed normal values of red blood cells, Total Leukocyte Count and an increase of the Erythrocyte Sedimentation Rate (ESR): 69 mm in 1h.

The hematoxylin and eosin-stained soft tissue section showed a subepithelial cleft formation. The
underlying connective tissue showed a diffuse infiltration of lymphoplasmocytes with abundant neutrophils creating microabcesses. DIF showed positive linear deposits of only IgA along the basement membrane in the epithelium. IgM, IgG, C3 and fibrinogen were negative in DIF. Subepithelial split with IgA positivity prompted the diagnosis of linear IgA disorder (Figure 5 A, B, C).

The therapeutic scheme was prednisolone (40 mg) for 2 weeks with monitoring of haematological values and evaluation of skin lesions. It was applied a local antifungal and antibacterial therapy to achieve a complementary therapeutic effect of corticosteroid drugs, supporting the healing of oral lesions (Figure 6 A, B). The maintenance of periodontal health and hygiene techniques were other determinants in the improvement
of the clinical picture. Doses were gradually lowered and discontinued when the lesions were completely healed. At the time of the last control, 9 months after its initial presentation, the patient no longer takes medication and remains asymptomatic, free of disease.

**DISCUSSION**

The LIgAD is an autoimmune bullous disease of systemic compromise, with dermatological and stomatological interest. The low incidence of this entity in our region is different from that reported by other authors. It seems to be more frequent in countries such as China, Malaysia, Thailand and less frequent in places like England. In a series of cases reported in Denmark, the data could demonstrate an increase of the incidence in the Scandinavian region. The authors explained that this phenomenon may be due to the lack of consensus in the diagnosis of bullous diseases as well as to an underestimation of the incidence rate of the pathology.

In South America, there are few works which have recorded the incidence of LIgAD. The series of cases from Chile and some reports from Brazil have shown few recorded cases. This is the first report in the region, of a clinical case where the main clinical features involved predominantly the oral mucosa. Caballero-Escuti et al., in their series of cases, described three patients of our city, two of them with cutaneous lesions and one with mucocutaneous manifestations. The small number of publications of this entity in our country, could be related, like the report of Lings and Bygum from Denmark, to the lack of diagnostic consensus of these lesions among the different scientific societies and the underdiagnoses of bullous diseases with oral involvement.

The aetiology of LIgAD is still discussed. The cases reported in current literature are, predominantly lesions triggered by drugs, being vancomycin the most frequent associated drug. In our case, the patient emphasized the appearance of the lesions after a dental implant surgery. At that time, the post-surgical medication was Amoxicillin and Diclofenac. We did not have the certainty if the lesions could be generated by drugs or surgical trauma. There are reports of pediatric LIgAd associated with the consumption of Amoxicillin and Clavulanic Acid, resolving with only the cessation of drug administration. In addition, Non-steroidal anti-inflammatories are included as possible triggers of this entity such as naproxen and diclofenac. Interestingly, prior studies have noted the importance of the relationship between bullous lesions, specially Pemphigoids, and mechanical trauma, surgeries, amputations, radiotherapy or ultraviolet exposure. The mechanism which could establish the relationship between a mechanical or surgical injury and bullae formation is still unclear. These external stimuli would represent a tissue injury and could activate the complement system and the subsequent bullous formation.

Another mechanism previously described was associated with local changes generated during the healing of surgical wounds, allowing the availability of the antigen presentation at the previously damaged site. The epithelial damage was also described as a stimulus of antibodies synthesis for local antigens and the subsequent sectorized outbreak of new lesions.

In order to improve the clinical provisional diagnosis of bullous diseases (Pemphigus Vulgaris and Pemphigoid subtypes), the Nicolsky sign (NS) is used to evidence the formation of blisters, demonstrating a weakness in the junction of the epithelium, chorion or other histologic structures. This sign allows to show the

![Figure 6. A) The palatal area was the most rebel against corticosteroid treatment. B) Periodontal therapy and oral hygiene techniques contributed to achieving the total healing of oral lesions.](image-url)
breakability of the tissue close to the blisters or even in the unblistered skin or mucosa. NS could be evidenced in Pemphigus Vulgaris as well as in some pemphigoids. However, in some cases NS is difficult to assess due to the oral mucosa inaccessibility. To simplify this procedure, it could be used a rubber bulb from a dropper, placed on the healthy mucosa for ten minutes. The negative pressure exerted on the tissue acts as a stimulus for the development of new bullous lesions. Once the existence of a new-blister has been corroborated, a dental sickle scaler is placed tangentially to the newformed blister to objectify its formation. This technique, described by Grinspan is a suitable tool to evidence the neoformation blisters during the provisional diagnosis of bullous diseases of the oral mucosa.

Oral microenvironment field antisepsis prior to performing the diagnosis biopsy using antifungal and local antiseptic therapy improves the symptoms. In this way, it was previously reported that the presence of oral ulcers or microerosions could generate ideal conditions for fungal colonization. Kurnatowska reported 93.7% patients with Oral Candidiasis referred burning mouth sensation, as well as a statistically significant association with those patients who presented atrophic lesions, redness and previous ulcers of the oral mucosa. For that reason, the ideal scenario previous the diagnosis biopsy should be free of microbial colonization. The relationship between poor periodontal status and oral bullous diseases has been previously reported. Periodontal therapy, as well as hygiene techniques education, improves the evolution of the lesions, decreasing the associated pain.

In our case, the patient showed a significant improvement of the lesions, with mouth rinses of 0.12% Chlorhexidine. The local treatment prior the biopsy not only optimized the post-surgical healing but also, generated better conditions for the histopathological diagnosis as the specimen was exempt from inflammatory signs possibly associated with fungal or bacterial colonization.

Previous reports, have described the incidence of the adult subtype of LIGAD among 60 and 65 years and a female predominance. Palate and buccal mucosa are the regions with the highest frequency of oral involvement. When the lesions involved skin, the trunk, extremities and perineum are the most frequently sites. Ocular involvement was reported in 50% of cases with the presence of scarring synechiae and conjunctival hyperaemia pain and photosensitivity in both eyes. His visual acuity was light perception (LP). In this case, the patient was a male and the skin lesions involved the frontal region and scalp. In addition, the ocular involvement was present with a fibrous flange in the external eye angle that clinically corresponded with a synechia. The patient also presented a generalized erythema of the conjunctival mucosa. These findings were previously described in cases of LIGAD with ocular involvement.

Regarding oral lesions, is remarkable that neither in this case nor in most cases considered for this review, the tongue involvement was present, being a differential diagnosis with other bullous lesions such as Pemphigus Vulgaris. Karagöz et al. reported the lingual mucosa in the second place of incidence of oral lesions between patients with Pemphigus Vulgaris, being buccal mucosa the main site of presentation. In our case, oral lesions were predominantly in hard and soft palate with a generalized redness of these areas. According to Joseph et al, this clinical phenotype is associated with a drug-induced scenario. Our case had many similarities to that presented by this author. The floor of the mouth was a region involved in our case, being an uncommon site of presentation of LIGAD.

In relation to histopathological diagnosis, we prefer to take a biopsy of a neoformation blister created by the rubber bulb technique. Histologically, LIGAD is characterized by the presence of subepithelial bullae with a dense infiltrate of neutrophils, eosinophils and lymphocytes.

The presence of neutrophil-microabscesses in the dermal papillae could be also observed. The basement membrane deposit of IgA in a linear pattern evidenced by DIF was the weightiest feature for diagnosis. DIF can also verify the negativity for other immunoglobulins and fibrinogen, distinguishing this entity from other bullous diseases.

In relation to the therapeutic scheme, dapsone is considered the first therapeutic line. However, there are other treatments associated with corticosteroids. In this case, systemic steroid treatment was agreed with dermatology. Systemic and local prednisolone was provided, emphasizing a rigorous control of the periodontal state and fungal colonization throughout the treatment. The evolution of the patient, fortunately, was outstanding with a decrease in symptoms and total remission of the lesions.

Finally, our experience supports the requirement of the oral microflora control in bullous diseases, before, during and after the diagnosis, which greatly improves the effectiveness of the treatment. FID is mandatory for diagnosis of bullous diseases with oral involvement.
CONCLUSION

This case represented a diagnosis challenge of an infrequent mucocutaneous entity of dermatological, ophthalmological and stomatological interest associated with a dental implant surgery procedure. We emphasized the need for more clinical reports in our region of bullous disorders as well as therapeutic schemes and its effectiveness in the patient outcome.

Since most of trigger factors are associated with daily clinical practice (e.g.: drugs, surgical injuries), they must be always carefully recorded in future works.

DISCLOSURES

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