

Inflammatory Fibrous Hyperplasia Associated with Chondroid Metaplasia – Report and Morphological Analysis of Five Cases

Hiperplasia Fibrosa Inflamatoria Asociada a Metaplasia Cartilaginosa -
Reporte y Análisis Morfológico de Cinco Casos

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ABSTRACT: Inflammatory fibrous hyperplasia (IFH) is a common reactive lesion in dental prostheses users that may be associated with chondroid metaplasia (CM). Metaplasia is an adaptive cellular process that may be caused by trauma. We reported here five cases of IFH associated with CM and analyzed morphologically the deposition of collagen in these lesions. Patients had a mean age of 58.8 years-old and were ill-fitting dental prostheses users. They presented nodular lesions located in the anterior maxilla. Microscopically, it was observed hyperplastic fibrous connective tissue with chronic inflammatory infiltrate and hyaline cartilage. No morphological differences were observed in collagen deposition under light microscopy, but quantitative analysis revealed a significantly higher collagen deposition at the connective tissue near CM ($p = 0.015$). IFH associated with CM affects ill-fitting dental prostheses users. The presence of CM is not significant to the lesion prognosis. However, its formation and the higher collagen deposition near it reinforces the IFH reactive origin.

KEY WORDS: hyperplasia, metaplasia, collagen, dental prosthesis, gingiva.

INTRODUCCIÓN

Inflammatory fibrous hyperplasia (IFH) is a common reactive lesion of the oral mucosa, which can occur due to constant trauma or poor oral hygiene. Clinically, it often presents as a nodular lesion with a firm consistency and normal color in the gingiva (Buchner *et al.*, 2010; Vidyanath *et al.*, 2015; Babu & Hallikeri, 2017). Although the clinical diagnosis of IFH is simple, the final diagnosis is established through histopathological analysis since several gingival reactive lesions perform clinical differential diagnosis with IFH. Microscopically, this lesion exhibits hyperplastic fibrous connective tissue as well as a variable amount of chronic inflammatory infiltrate (Schmidt *et al.*, 2016; Babu & Hallikeri, 2017).

Constant cell stress, resulting from trauma and inflammation, may cause a reversible adaptive process called metaplasia. This process can be interpreted as an attempt by the organism to replace a differentiated somatic cell type exposed to stress into another better-suited differentiated somatic cell type to its environment. In this way, the cells in the connective tissue may develop adipose, chondroid, or osseous metaplasia (Slack, 2007; Giroux & Rustgi, 2017). Chondroid metaplasia (CM) is uncommon in the oral cavity and, in rare instances, may be associated with IFH (Cutright, 1972; Tenorio *et al.*, 2016). In this context, the objective of this paper is to report five cases of IFH associated with CM and to

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analyze morphologically the deposition of collagen in these lesions.

CASE REPORTS

Case 1. A female patient, 46-years-old, presented an asymptomatic exophytic nodular lesion in the anterior region of the superior alveolar ridge, sessile, measuring about 1.0 cm, with smooth consistency, and normal color. The lesion has grown slowly over 4-months and patient was using an ill-fitting dental prosthesis. The clinical diagnosis of fibrous hyperplasia was established, and an excisional biopsy under local anesthesia was performed. The histopathological analysis revealed a reactive lesion coated with keratinized stratified squamous epithelium exhibiting hyperplasia, hydropic degeneration, spongiosis, and exocytosis. The hyperplastic fibrous connective tissue had an intense chronic inflammatory infiltrate, and it was also observed the presence of hyaline cartilage. The final diagnosis of IFH associated with CM was established, and the patient did not show any signs of recurrence.

Case 2. A male patient, 57-years-old, exhibited an asymptomatic exophytic nodular lesion in the anterior region of the superior alveolar ridge measuring about 0.6 cm, with firm consistency, and normal color. The patient was using an ill-fitting dental prosthesis and reported that the lesion had grown slowly over 2-months. In this way, the clinical hypothesis was of fibrous hyperplasia, and an excisional biopsy under local anesthesia was performed. Microscopically, it was observed oral mucosa overlaid with keratinized stratified squamous epithelium exhibiting hyperplasia, hydropic degeneration, spongiosis, and exocytosis, while the hyperplastic fibrous connective tissue had a mild chronic inflammatory infiltrate and the focal formation of hyaline cartilage. Thus, the final diagnosis of IFH associated with CM was rendered, and the patient did not show any signs of recurrence.

Case 3. A female patient, 59-years-old, showed an asymptomatic lesion in the anterior region of the superior alveolar ridge. Clinically, the lesion was nodular sessile, with smooth consistency, and normal color, and measuring about 6.0 cm. The patient was using an ill-fitting dental prosthesis. The clinical diagnosis of fibrous hyperplasia was established, and an excisional biopsy under local anesthesia was

performed. The microscopic analysis revealed oral mucosa overlaid with keratinized stratified squamous epithelium exhibiting hydropic degeneration, spongiosis, and exocytosis. The dense fibrous connective tissue was hyperplastic and had an intense chronic inflammatory infiltrate and a focal formation of hyaline cartilage, thus, the diagnosis of IFH associated with CM was established. The patient did not show any signs of recurrence.

Case 4. A female patient, 63-years-old, presented an asymptomatic exophytic nodular lesion in the anterior region of the superior alveolar ridge, measuring about 1.0 cm, with smooth consistency, and normal color. Due to the use of an ill-fitting dental prosthesis, the clinical hypothesis was of fibrous hyperplasia, and an excisional biopsy under local anesthesia was performed. The histopathological analysis revealed a lesion overlaid with keratinized stratified squamous epithelium exhibiting hydropic degeneration, spongiosis, and exocytosis, as well as hyperplastic fibrous connective tissue, which had an intense mononuclear inflammatory infiltrate. The presence of hyaline cartilage was also observed. In this way, the histopathological diagnosis of IFH associated with CM was established, and the patient did not show any signs of recurrence.

Case 5. A female patient, 69-years-old, presented an asymptomatic nodular lesion in the anterior region of the superior alveolar ridge with firm consistency, normal color, and measuring about 0.8 cm (Fig. 1A). The associated etiological factor was the use of an ill-fitting dental prosthesis. Due to the consistency of the lesion, a panoramic radiograph was requested but it showed no noteworthy alterations (Fig. 1B). Thus, a clinical diagnosis of fibrous hyperplasia was rendered, and an excisional biopsy under local anesthesia was performed. Microscopically, it was observed oral mucosa overlaid with keratinized stratified squamous epithelium exhibiting hyperplasia, hydropic degeneration, spongiosis, and exocytosis. The dense fibrous connective tissue was hyperplastic and had an moderate chronic inflammatory infiltrate as well as the formation of hyaline cartilage (Fig. 2). So, the final diagnosis of IFH associated with CM was rendered, and the patient did not show any signs of recurrence.

Morphological Findings. For morphological analysis of collagen fibers deposition, FIH was assessed on Masson's trichrome-stained slides, and the quantification was estimated on captured images and

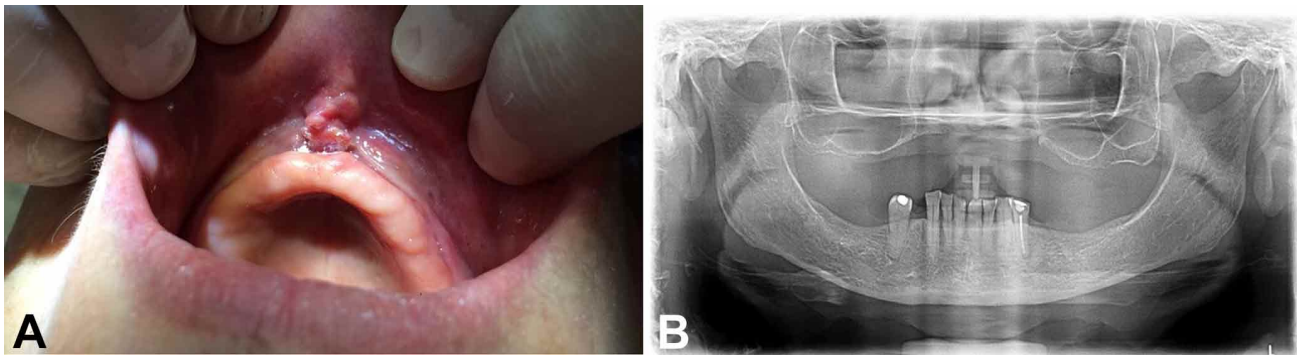


Fig. 1. Clinical and radiographic aspect (A) Clinical aspect – Exophytic nodular lesion in the anterior region of the superior alveolar ridge. (B) Panoramic radiograph with no noteworthy alterations.

visualized on ImageJ® software (version 1.8.0; NIH, USA) following the protocol previously proposed by Chen *et al.* (2017). Thus, the amount of collagen was recorded as a fraction area of the adjusted threshold value of green color within the region of interest. In each case were randomly selected three hyperplastic fibrous connective tissue fields corresponding to areas of the FIH as well as of the connective tissue surrounding the CM. Areas of connective tissue without hyperplasia was used as a reference for collagen deposition. The morphological data were statistically analyzed using the non-parametric Mann-Whitney test

to compare the median percentages of collagen deposition between the groups. A statistical 5 % significance level ($p \leq 0.05$) was considered, and the analyses were carried out using Statistical Package for the Social Sciences (SPSS 22.0; IBM Corp., USA). No morphological differences were observed in collagen deposition under light microscopy in hematoxylin and eosin or Masson's trichrome stained slides (Fig. 3). However, the quantitative analysis revealed a significantly higher collagen deposition at the connective tissue surrounding the CM ($p = 0.015$) (Fig. 4).

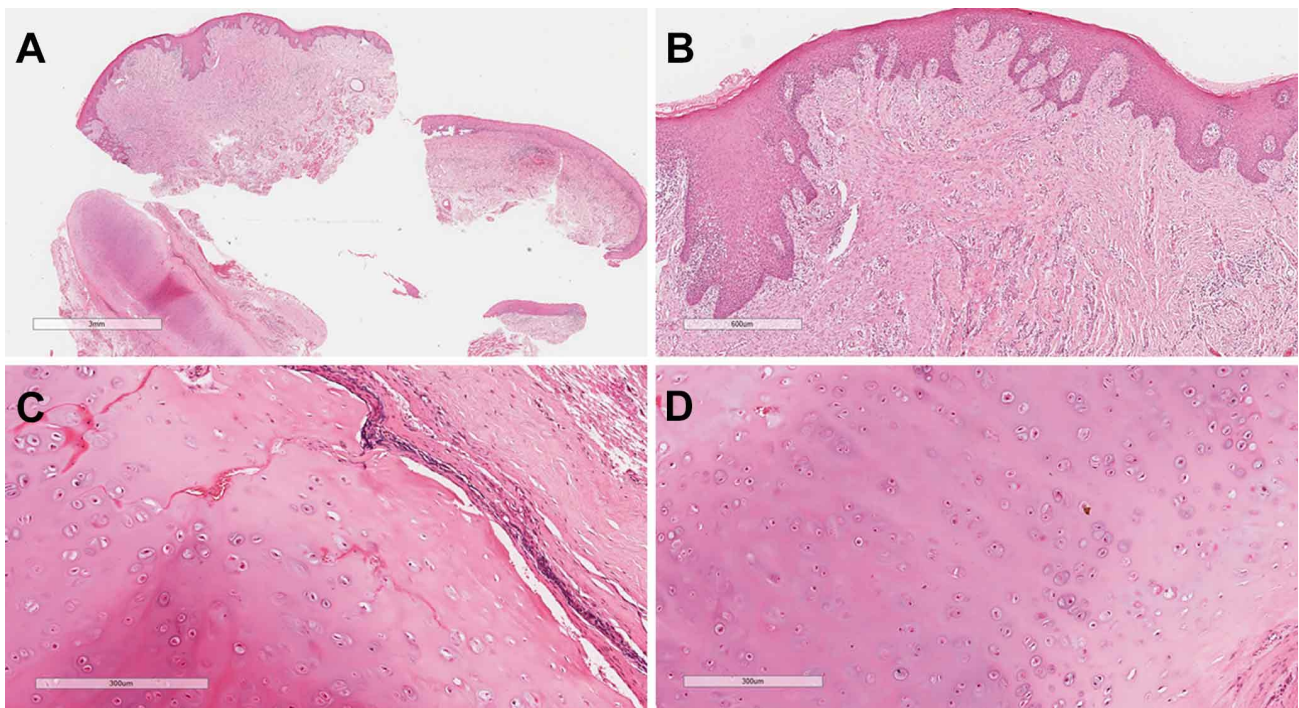


Fig. 2. Histopathological features (Hematoxylin and Eosin) (A) Benign reactive lesion associated with chondroid metaplasia. (B) Oral mucosa lined by hyperplastic keratinized stratified squamous epithelium and hyperplastic dense fibrous connective tissue exhibiting moderate chronic inflammatory infiltrate. (C) Chronic inflammatory infiltrate surrounding the chondroid tissue. (D) Structural and cellular normality of hyaline cartilage [Scale bars: A – 3 mm; B – 600 μ m; C and D – 300 μ m].

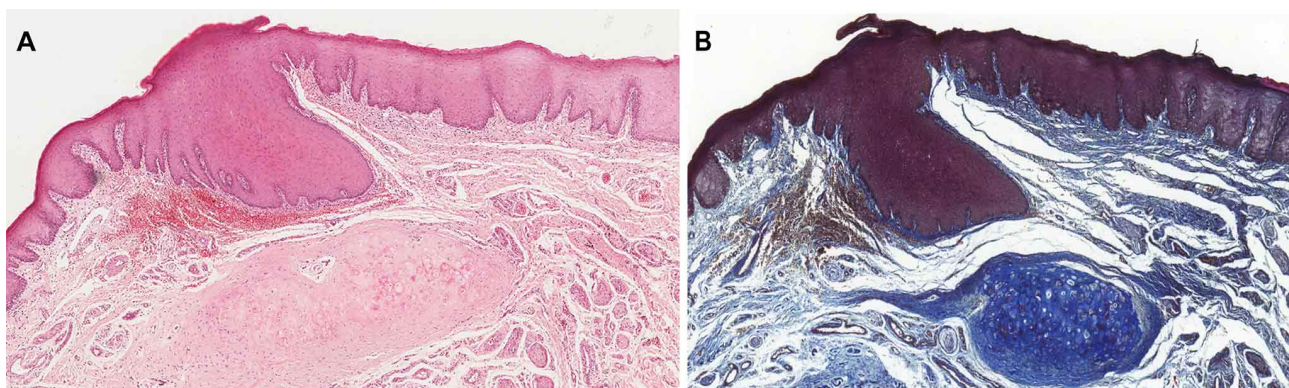


Fig. 3. Inflammatory fibrous hyperplasia associated with well-circumscribed hyaline cartilage. No microscopic difference is observed in the collagen deposition between (A) a hematoxylin and eosin stain and (B) Masson's trichrome stain [Magnification x10].

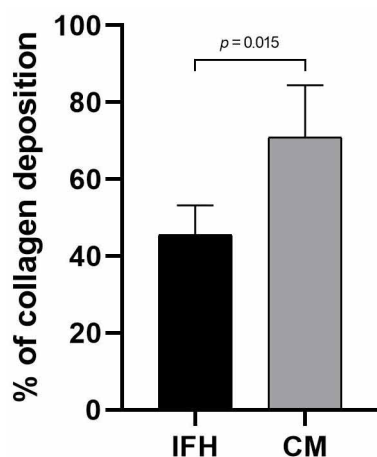


Fig. 4. Median of the percentages for collagen deposition and interquartile range. There was a significantly higher collagen fibers deposition in the connective tissue surrounding the chondroid metaplasia (CM) than in the hyperplastic connective tissue of inflammatory fibrous hyperplasia (IFH).

IFH caused by ill-fitting dental prostheses may present different morphological findings, such as the presence of chondroid or osseous metaplasia in the fibrous connective tissue (Cutright, 1972; Filgueiras *et al.*, 2016; Tenorio *et al.*, 2016). In the present cases, it was observed that all patients were ill-fitting removable dental prostheses users, being this the etiological factor associated with the rise of the lesions.

IFH associated with CM was initially described by Cutright (1972) that observed a higher occurrence of these lesions in the anterior maxilla, between the first premolars of female patients aged from 24 to 73 years-old. Furthermore, this author reported that these lesions exhibited a clinical aspect that ranged from a slightly raised to a polypoid lesion with a pale or reddened color and firm consistency, which may also show areas of ulceration. Thus, due to its clinical aspects, IFH associated with CM performs clinical differential diagnosis with other reactive lesions, such as pyogenic granuloma, peripheral giant cell granuloma, and peripheral ossifying fibroma (Buchner *et al.*, 2010; Babu & Hallikeri, 2017). Similarly, our cases were in female patients with a mean age of 58.8 ± 8.4 years-old (range: 46 - 69). Also, all lesions were located in the anterior region of the maxilla and had a normal color nodular clinical aspect with a smooth or firm consistency.

DISCUSSION

Reactive gingival lesions are relatively common and may comprise 3.6 % to 6.7 % of the lesions of the oral mucosa. Overall, IFH is the most frequent (47 %) in this group and shows a higher occurrence in females between the third and fourth decade (Buchner *et al.*, 2010; Babu & Hallikeri, 2017). The etiology of IFH is strongly associated with chronic low-grade trauma, which can generate local inflammatory processes, being observed a higher occurrence in dental prosthesis users. Interestingly, some cases of

Microscopically, Cutright (1972) observed that these lesions exhibited loose fibrous connective tissue or dense collagenized connective tissue, which could include cartilaginous or bone tissue and areas of calcification. This author also described that chondroid metaplasia usually resembled hyaline cartilage and that fusiform cells from surrounding mesenchymal tissue showed gradual differentiation to oval or round cells, which were trapped in an amorphous and eosinophilic intercellular material as they became more mature. Except for the presence of calcifications and osseous metaplasia, these morphological features corroborate the histopathological findings of the present cases.

Due to its morphological features, IFH associated with CM performs differential diagnosis with chondroma and cartilaginous choristoma since these lesions may also be microscopically characterized by the presence of hyaline cartilage. However, the clinical history of the lesion is essential for establishing the diagnosis given chondroma and cartilaginous choristoma, contrary to the IFH associated with CM, do not present local trauma as an etiopathogenic factor. Besides that, the first one is defined as a benign neoplasm and the second consists of the presence of a cohesive and well-organized growth of normal cells/tissue in an abnormal location, while IFH associated with CM is characterized as a reactive lesion (Tenorio *et al.*, 2016; Bosotti *et al.*, 2019; Dimitrijevic *et al.*, 2019; Sethi *et al.*, 2020).

As an adaptive cellular process, metaplasia tends to occur in tissues constantly exposed to traumatic, infectious agents or abnormal hormonal stimuli, which change the cell morphological features to another that belongs to the same germ layer (Slack, 2007; Giroux & Rustgi, 2017). In the present cases, we observed that the spindle cells present in the connective tissue acquired phenotypic features of chondrocytes, which promoted the morphological alteration of the local connective tissue to a cartilaginous tissue. It is known that fibroblasts are capable of differentiating into chondrocytes since both cell types originate from the mesoderm. Also, when acquiring the chondroid phenotype, these cells reduce the synthesis and secretion of collagen type I and become capable of producing an extracellular matrix rich in collagen type II and chondroitin sulfate, which may stimulate and reinforce the differentiation process in its adjacent mesenchymal cells (Annamalai *et al.*, 2016; Grath & Dai, 2019).

Our morphological analysis, under light microscopy, did not show differences in collagen deposition between the hyperplastic connective tissue of the IFH and the connective tissue that surrounded the CM. However, in the quantitative analysis, significantly higher collagen deposition was observed in the connective tissue adjacent to the hyaline cartilage. This difference may be justified by the fact that the connective tissue near CM possibly constitutes a transition zone where there is the presence of fibroblasts and chondroid phenotype cells, which synthesis collagen types I and II, respectively. Besides that, fibroblasts also can secrete collagen type III, a type of collagen that often consists

of pro-collagen, intermediate collagen, or collagen with pathological alterations (Schmidt *et al.*, 2016; Grath & Dai, 2019). In this way, we believe that this histological finding reinforces the reactive origin of this lesion.

The treatment for IFH associated with CM is total excision of the lesion since there are no reports of recurrences or post-surgical complications. Besides that, it is necessary to make a new dental prosthesis to remove the traumatic factor that causes the rise of the lesion (Filgueiras *et al.*, 2016; Tenorio *et al.*, 2016). In this context, it is essential to recognize the clinical and histopathological features of IFH associated with CM to perform an accurate diagnosis and avoid excessive and inappropriate treatments.

CONCLUSIONS

IFH associated with CM is uncommon and affects the anterior maxilla of ill-fitting dental prostheses users. Although the clinical diagnosis of IFH is simple, histopathological analysis is essential to establish the final diagnosis since this lesion may perform clinical and histopathological differential diagnosis with reactive lesions as well as neoplastic and choristomatous lesions. Also, the presence of CM is not significant to the lesion prognosis. However, this histological finding reinforces the reactive origin of IFH since CM constitutes a process of cellular adaptation caused by constant local trauma, which also induces a higher collagen deposition in CM surrounding connective tissue.

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RESUMEN: La hiperplasia fibrosa inflamatoria (HFI) es una lesión reactiva común en los usuarios de prótesis dentales que puede estar asociada con la metaplasia cartilaginosa (MC). La metaplasia es un proceso celular adaptativo que puede ser causado por un trauma. El presente informe analizó cinco casos de HFI asociados a MC y se analizaron morfológicamente la deposición de colágeno en estas lesiones. Los pacientes tenían una edad media de 58,8 años y eran usuarios de prótesis dentales mal adaptadas. Se observaron lesiones nodulares localizadas en la parte anterior del maxilar. Microscópicamente se observó tejido conectivo fibroso hiperplásico con infiltrado inflamatorio crónico y cartílago hialino. No se observaron diferencias morfológicas en la deposición de colágeno bajo microscopía óptica, pero el análisis cuantitativo reveló una deposición de colágeno significativamente mayor en el tejido conectivo cerca de MC ($p = 0,015$). La HFI asociada con la MC afecta a los usuarios de prótesis dentales mal adaptadas. La presencia de MC no es significativa para el pronóstico de la lesión. Sin embargo, su formación y la mayor deposición de colágeno cerca de MC refuerza el origen reactivo de HFI.

PALABRAS CLAVE: hiperplasia; metaplasia; colágeno; prótesis dentales.

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