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Giant cell tumor of the bone of maxillary sinus: A rare uncommon manifestation implicated in a new mosaic of disorders?

Tumor de células gigantes do osso do seio maxilar: Uma rara manifestação implicada em um novo modelo de desordens?

Tumor óseo de células gigantes del seno maxilar: ¿Una rara manifestación implicada en un nuevo modelo de trastornos?

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Abstract

The goal is to show a rare case of Giant Cell Tumor of Bone in the maxillary sinus implicated in a process coincidentally or casually with another type of lesion primarily developed. A 33-year-old male patient attended a surgical service, presenting swelling, obstruction and firm mass externalizing through the right nostril and perceived during 6 months. During the anamnesis, the patient stated to been underwent an incisional biopsy 4 years ago of a tumor with histopathological diagnosis of the Nasal Paraganglioma, however the immunohistochemical study was negative for this tumor. During the Computed Tomography evaluate was observed a hyperdense mass occupying the entire maxillary sinus. In the Nuclear Magnetic Resonance evaluation, it was showed a hypersignal image in the entire maxillary sinus, invading the nasal cavity and portion of skull base. A bone window was performed in the right maxillary sinus and excisional biopsy was made. In the new histopathological examination, the diagnose was consistent with Giant Cell Tumor of Bone, being observed a large number of multinucleated giant cells, some with disorganized nuclei and others similar to Touton giant cells. A large proliferation of xanthomatous-looking cells was also observed without features of malignity. At the 3-year follow-up, the patient reported no complications such as facial paralysis, infection, relapse or spread. The association between lesions occurring in the same location requires further study, possibly implicated in a new model of clinical, microscopic, and genetic disorders. Thus, masses originating from chronic inflammatory tissue may have the potential to transform into GCTB?

Keywords: Giant cell tumor of bone; Maxillary sinus neoplasms; Head and neck neoplasms; Nasal cavity; Maxilla; Paranasal sinuses.

Resumo

O objetivo deste trabalho é relatar um raro caso de Tumor de Células Gigantes do Osso em Seio Maxilar implicado em um processo coincidentemente ou casualmente com outro tipo de lesão primariamente desenvolvida na região. Paciente, masculino, 33 anos, atendido no serviço de cirurgia bucomaxilofacial, apresentando tumefação, obstrução e uma firme massa externalizada pela narina direita com duração de 6 meses. Durante a anamnese o paciente relatou ter sido submetido a biópsia incisional 4 anos atrás, na mesma região, com diagnóstico de paraganglioma nasal, contudo o estudo imunohistoquímico foi negativo para este tumor. Na avaliação Tomográfica foi observado massa hiperdensa ocupando todo o seio maxilar. Na avaliação de Ressonância Nuclear Magnética foi observado também uma massa com hipersinal, invadindo a cavidade nasal e porção da base do crânio. Uma janela óssea foi realizada no seio maxilar direito e a biópsia excisional foi instituída. No novo exame histopatológico o diagnóstico foi consistente com Tumor de Células Gigantes do Osso, sendo observado um largo número de células gigantes multinucleadas, alguns com desorganização nuclear e outras similares às células gigantes de Touton. Larga proliferação de células xantomatosas também foi observado sem sinais de malignidade. Após 3 anos de proservação o paciente evoluiu sem complicações ou recidiva. A associação entre as lesões ocorrendo no mesmo lugar requer estudos mais aprofundados, possivelmente implicado em um novo modelo de desordens clinicas, microscopicas e genéticas. Sendo assim, massas originadas de tecidos cronicamente inflamados poderão ter o potencial de se transformarem em TCGO?
Palavras-chave: Tumor de células gigantes do osso; Neoplasias do seio maxilar; Neoplasia de cabeça e pescoço; Cavidade nasal; Maxila; Seios paranasais.

Resumen

El objetivo de este trabajo es reportar un caso raro de Tumor Óseo de Células Gigantes en Seno Maxilar implicado en un proceso coincidente o casualmente con otro tipo de lesión desarrollada primariamente en la región. Paciente masculino de 33 años de edad, atendido en el servicio de cirugía oral y maxilofacial, con tumefacción, obstrucción y masa firme exteriorizada por fosa nasal derecha de 6 meses de evolución. Durante la anamnesis, lo paciente refirió haber sido sometido a biopsia incisional hace 4 años, en la misma región, con diagnóstico de paraganglioma nasal, sin embargo el estudio inmunohistoquímico fue negativo para este tumor. En la tomografía computarizada se observó una masa hiperdensa que ocupaba todo el seno maxilar. En la evaluación de resonancia magnética también se observó una masa con hiperseñal que invadía la cavidad nasal y parte de la base del cráneo. Se realizó una ventana de hueso en el seno maxilar derecho y se instituyó una biopsia excisional. En el nuevo examen histopatológico el diagnóstico fue compatible con Tumor Óseo de Células Gigantes, observándose un gran número de células gigantes multinucleadas, algunas con desorganización nuclear y otras similares a las células gigantes de Touton. También se observó una amplia proliferación de células xantomatosas sin signos de malignidad. Después de 3 años de seguimiento, el paciente evolucionó sin complicaciones ni recurrencia. La asociación entre lesiones que ocurren en el mismo lugar requiere más estudios, posiblemente implicados en un nuevo modelo de trastornos clínicos, microscópicos y genéticos. Entonces, ¿las masas que se originan en tejidos crónicamente inflamados podrían tener el potencial de transformarse en TCGO?
Palabras clave: Tumor óseo de células gigantes; Neoplasias del seno maxilar; Neoplasia de cabeza y cuello; Cavidad nasal; Maxilar; Senos paranasales.

1. Introduction

Giant cell tumor of the bone (GCTB) is an uncommon, benign, locally aggressive lesion that most frequently affects the epiphysis of long bones, especially around the knee (Montgomery et al., 2019). The epiphyseal region is a common site for the development of GCTB; however, the lesion may also frequently occur in other regions including the distal femur, proximal tibia, distal radius, and sacrum (Rosa et al., 2018; Sobti et al., 2016). Although rarely reported in the bones of the head, manifestations in bones developing from endochondral ossification have been observed, such as the sphenoid, ethmoid, and temporal bones, and almost exclusively involved (Mohaidat et al., 2019). In the gnathic bones, clinical appearance may vary due to dental root resorption, bone destruction, pain, pathological fractures, and/or metastatic spread (Sobti et al., 2016).

GCTB exhibits clinically aggressive behavior with rapid growth—sometimes in weeks and causing few symptoms—that leads to thinning and rupture of cortical bone and invasion of adjacent soft tissues, although not invading or ulcerating the skin and subcutaneous tissue (di Carlo et al., 2020). GCTB is categorized among benign tumors; however, some studies have preferred to characterize it as possessing “intermediate malignant potential” due to its osteolytic properties causing invasion and destruction of adjacent structures (di Carlo et al., 2020).

The treatment of GCTB depends on its aggressiveness. Surgical resection, embolization, bisphosphonates, anti-receptor activator of nuclear factor-kappaB ligand antibody (i.e., RANKL) therapy, chemotherapy, and radiotherapy can be used (Sobti et al., 2016). Currently, the use of denosumab has gained prominence as an adjuvant therapy owing to the inhibitory effects on RANKL, promoting significant reduction in tumor size, restoration of bone stock, and significant pain reduction in treated patients (Luengo-Alonso et al., 2019).

A comprehensive differential diagnosis should include tumors with similar histological appearance, as well as benign or malignant epithelial neoplasms with common chronic inflammatory conditions in the gnathic bones, nasal cavity, and paranasal sinuses, such as brown tumors of hyperparathyroidism, malignant fibrous histiocytoma, giant cell central granuloma, and chronic inflammatory masses occurring in the nasal cavity (Board WC of TE, 2020; Wülling et al., 2001).

In this context, we present a rare clinical case of GCTB involving the right maxillary sinus extending to the nasal cavity and skull base and implicated in a coincidental or causal process with another type of lesion that previously developed in the same location.

2. Methodology

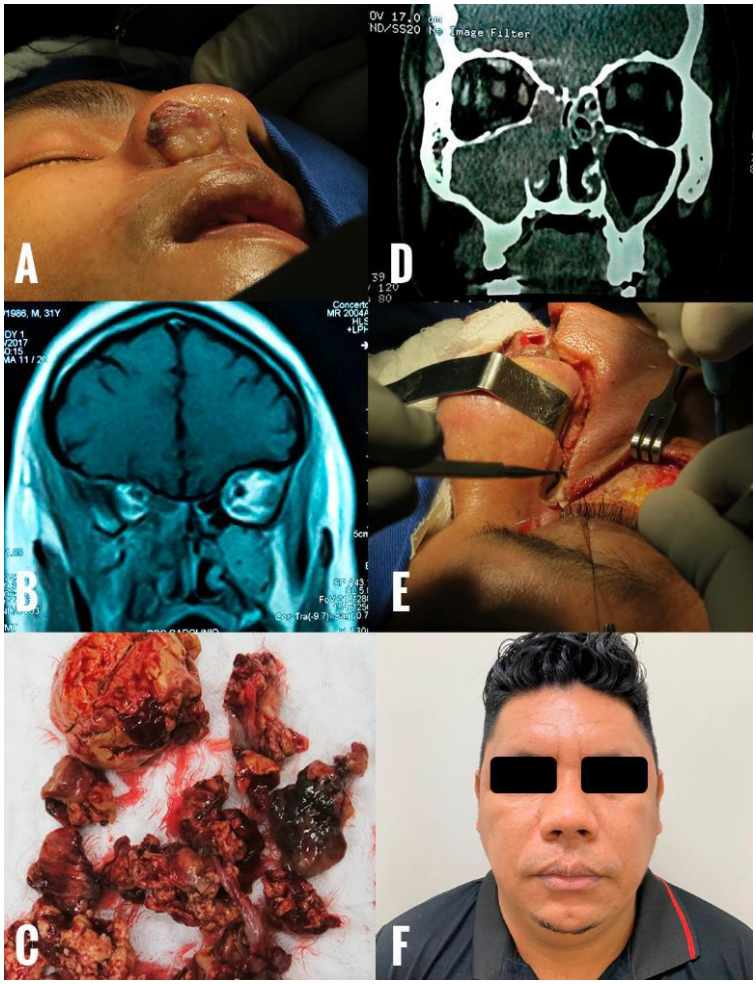
This is a qualitative and descriptive study, in which a rare case of giant cell tumor of bone is reported. All procedures in this study were performed in accordance with the ethical standards of the Institutional Research Committee of Adriano Jorge Hospital Foundation (Brazil, document number 51303221.0.0000.0007) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The patient provided written consent for publication of anonymized case details (TCLE)

3. Case Report

A 33-year-old male patient presented to the oral and maxillofacial surgery service complaining of a 6-month history of painful swelling, obstruction, and bleeding in the nasal cavity. Physical examination revealed a firm mass that obliterated and externalized through the right nasal cavity, with intact skin and no ulceration (Figure 1a). The patient reported a medical history of undergoing an incisional biopsy 4 years previously in the same region, with a histopathological diagnosis suggestive of nasal paraganglioma. Furthermore, immunohistochemical investigation of this tumor was negative and consistent with polypoid tissue exhibiting a robust inflammatory process with numerous interspersed multinucleated giant cells, with positivity for AE1/AE3 and CD68 markers (Table 1) (Figure 2a, 2b, 2c). Due to distance, difficulties with mobility, and financial issues, the patient was unable to attend the referral hospital, and did not return to subsequent appointments and did not undergo proper treatment for the first lesion. The new Computed tomography (CT) revealed a hyperdense mass occupying the entire maxillary sinus, with no signs of aggressive resorption, perforation, or tissue spread (Figure 1d). Nuclear magnetic resonance (NMR) imaging revealed a hyperintense mass occupying the right maxillary sinus obliterating the right nasal cavity and extending to the skull base (Figure 1b). A bone window was created in the right maxillary sinus through a Weber-Ferguson incision, and an excisional biopsy of the mass was performed. The osteotomy was reduced and fixed using plaques and 2.0 mm screws, and the surgical specimen was submitted to anatomopathological analysis (Figure 1c, 1e). The patient has not undergone any adjuvant therapy and has been followed up for 3 years with no signs of recurrence or complications (Figure 1f). Grossly, the surgical specimen exhibited a dark brown-to-reddish appearance with a friable texture (Figure 1c). The new histopathologic examination revealed a benign neoplasm characterized by a highly cellular tumor dominated by large numbers of osteoclast-like giant cells. Multinucleated giant cells exhibited variable numbers of nuclei, some with > 20 nuclei per cell, with nuclei arranged in a disorganized pattern in most giant cells. Some areas exhibited multinucleated giant cells with a ring of nuclei surrounding a central homogeneous cytoplasm, similar to Touton giant cells. The cytoplasm surrounding the nuclei was both

amphophilic and eosinophilic, whereas the cytoplasm near the periphery of the cell was pale and foamy in appearance. The mononuclear cells exhibited varied morphologies, including round-to-oval cells and spindled cells in a fibrotic background in most areas. In some fields, the presence of a large proliferation of periodic acid-Schiff-positive xanthoma cells was evident. Proliferation of vascular spaces and hemorrhages completed the analyzed fields. No atypical mitotic figures or necrosis were observed, nor features of malignancy, such as significant nuclear atypia or necrosis. The diagnosis was consistent with GCTB (Figure 3a-3f).

Figure 1 - A) Clinical appearance of the tumor, externalizing through right nostril. B) NMR showing a hypersignal mass occupying the right maxillary sinus, obliterating the right nasal cavity and extending to skull base. C) Macroscopy appearance of the tumor. D) CT showing a hyperdense mass occupying the entire right maxillary sinus. E) Weber-Ferguson incision to perform bone window. F) 3-year follow-up, with no complications such as facial paralysis, infection, relapse or spread.



Source: Authors.

Figure 2 - A) First histopathologic exam with suggestive diagnostic of Paraganglioma, showing a mass consisting of strands of rounded cells, with eosinophilic cytoplasm, oval nuclei, and some areas of hemorrhage and necrosis. **B)** CD68 positive marker showing macrophage activity and some interpose multinucleated giant cells, in the first biopsy. **C)** H3.3G34W negative marker showing no activity for GCTB 4 years ago.

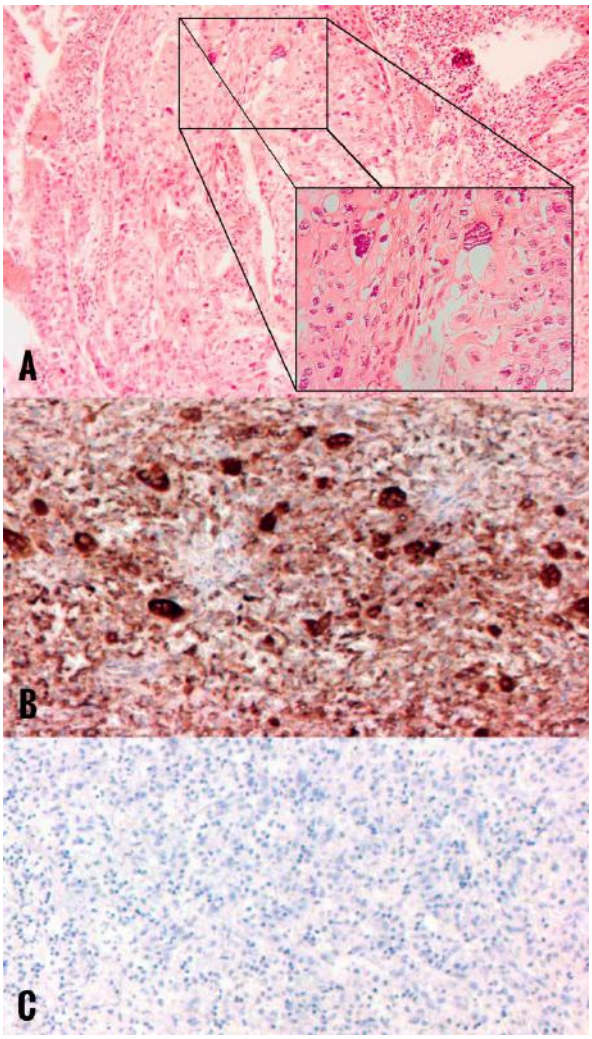


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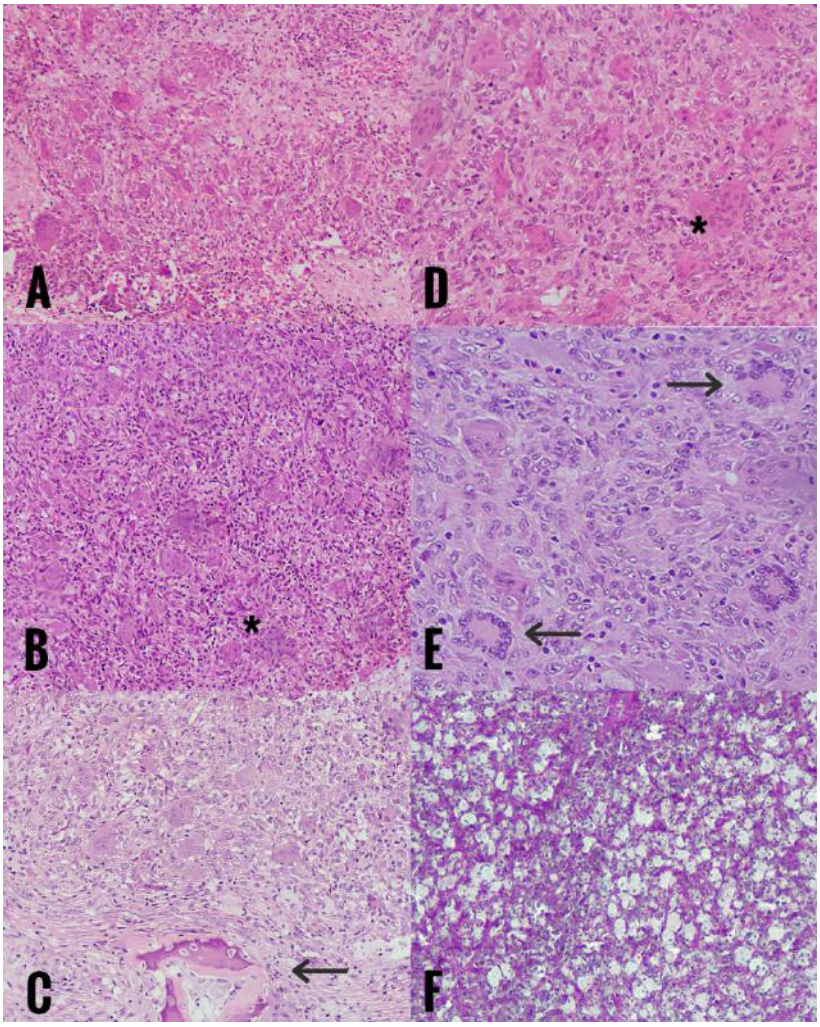
Table 1 - Immunohistochemical result of the polypoid mass lesion in the present case from the first incisional biopsy 4 years ago.

Antibody	Clone	Result
Cytokeratin (40, 48, 50 and 50,6 kDa)	AE1/AE3	**Positive**
CD68	K-P1	**Positive**
Desmin	D33	Negative
CD34	QBEnd 10	Negative
S-100 Protein	Polyclonal	Negative
Smooth Muscle Actin	1A4	Negative
Chromogranin A	DAK-A3	Negative
Synaptophysin	DAK-SYNAP	Negative
Succinate Dehydrogenase Subunit B	21A11AE7	Negative
H3.3G34W	RM263	Negative

Source: Authors.

Figure 3 - New histopathological features of the surgical specimen 4 years after. This tumor was characterized by proliferation of vascular spaces and fibroblastic cells with discrete collagen fibers and areas of hemorrhage surrounded by a large number of multinucleated giant cells, some with disorganized nuclei (**A, B, C and D - asterisk**), others similar to Touton giant cells (**E - arrow**), and different areas with osteoid material (**arrow**). A large proliferation of xanthomatous-looking cells was also observed (**F**), positive for periodic acid–Schiff staining (PAS, x200).



Source: Authors.

4. Discussion

The World Health Organization classification of tumors defines GCTB as a primary intramedullary bone tumor composed of mononucleated cells and osteoclast-like multinucleated giant cells, presenting as a locally aggressive lesion with unpredictable behavior (Board WC of TE, 2020). It is believed that the stroma represents the active portion of the tumor cells, capable of secreting differentiation factors that recruit monocytes, promote their fusion, and form the third cell type in CGTB—osteoclast-like multinucleated giant cells (Board WC of TE, 2020).

The stroma is composed of proteoglycans, glycoproteins, and water plays a fundamental role in the development of any benign or malignant pathological process. In GCTB, cytokines and differential factors, including monocyte chemoattractant protein-1, osteoclast differentiation factor, and macrophage colony-stimulating factor, are present, suggesting that these molecules are essential for the genesis of osteoclast-like multinucleated giant cells (Wülling et al., 2001). However,

several chronic inflammatory lesions with giant cell configurations may exhibit similar histopathological features, principally at the beginning of the disease process. In our case, the primary lesion that developed 4 years previously had already demonstrated positivity for the CD68 marker and low activity of multinucleated giant cells in between. We believe that the size of the incisional biopsy performed previously could have compromised global assessment of the lesion, thus masking important characteristics of its development. It is possible that this tumor may represent a giant cell tumor of the bone arising ectopically in this region. Although we cannot exclude this hypothesis, we do not have evidence to support this.

In some giant cells-rich cases the G34W mutation of H3F3A gene is useful for differential diagnosis because immunohistochemical (IHC) staining for H3F3A G34W in GCTB has a positive range of 94.7-100%. Due to its potential of transformation, GCTB have genetic alterations and express more important cytokine and differentiation markers than multinucleated giant cells. Because G34W mutations happen more frequently than chromosomal abnormalities and can be causative risk factors for chromosomal structural remodeling in DNA synthesis, we hypothesize that the polypoid mass remnant would have differentiating markers in its stroma that would become early precursors for the development of GCTB. (Basu et al., 2021; Noh & Parket al., 2018; Ud Din et al., 2020).

The World Health Organization describes the histological appearance of GCTB as a highly cellular lesion typically dominated by large numbers of non-neoplastic osteoclast-like giant cells, between which mononuclear cells are embedded. Giant cells exhibit a variable number of nuclei, with some having > 50 nuclei per cell. Mononuclear cells in GCTB exhibit a variety of morphological features, including round to oval cells in a fibrotic background and spindle cells associated with a fibrous matrix. The presence of atypical mitotic figures should raise suspicion for malignancy. In the present case, a large number of multinucleated giant cells were observed in all analyzed fields, with > 20 nuclei per cell. In addition, the cytoplasm of the mononuclear cells was epithelioid, with nuclei similar to those observed in multinucleated giant cells. The stroma was fibrous with associated spindle cells. However, atypical mitotic figures were not observed in this case. Furthermore, some areas contain hemorrhagic foci and a large number of xanthoma cells with abundant cytoplasm and fine vacuoles, which has also been reported in previous studies (Montgomery et al., 2019; Sobti et al., 2016; di Carlo et al., 2020; Tuluc et al., 2007).

Occasional Touton giant cells have been observed. Kumar et al. analyzed 68 cases of GCTB in the tendon sheath. Of these, osteoclast-like giant cells were uniformly observed in all cases, while only nine (13.2%) cases exhibited Touton-type giant cells, which confirms that this finding is not a common feature in these tumors (Kumar et al., 2018), its mechanism is not well understood, but it now seems to arise from the fusion of inflammation-resolving macrophages through an axis formed by macrophage colony- stimulating factor, IFN- γ, or IL-6 and monocytes fuse. (Brooks et al., 2019)

According to Amary et al., anti-histone H3.3G34W rabbit monoclonal antibody (clone RM263) is highly specific and sensitive for tumors and is a powerful immunohistochemical marker for GCTB, confirming biopsy specimens and supporting the final diagnosis, thus enabling discrimination of GCTB from its mimics, such as giant cell granulomas of the jaw, cherubism, brown tumors of hyperparathyroidism, and foreign body-type giant cell reaction (Amary F et al., 2018). We did not rule out the possibility of a GCTB in development due to a partial biopsy performed primarily; however, the immunohistochemical panel was negative for H3.3G34W and other markers and positive for CD34 and AE1/AE3.

The management of GCTB depends on its location and radiological features. Surgical resection is the universal standard of treatment for GCTB (Errani et al., 2018). Currently, denosumab is used as an adjuvant to suppress osteoclastic lineage cells and prevent bone destruction (Errani et al., 2018). Nevertheless, studies comparing different treatment methods with denosumab have reported an increased rate of recurrence (20% to 100%) using curettage with preoperative denosumab compared with curettage alone (0% to 50%) (Tsukamoto et al., 2020) These different results, associated with the long-term therapeutic effect of denosumab, may cause dramatic changes in the histological appearance of the tumor, nevertheless careful evaluation is necessary for its use (Kato et al., 2018). In a retrospective study evaluating different methods of treatment for

GCTB, was showed that aggressive intralesional curettage with hydrogen peroxide and filling up with bone cement raises relapse rates. The use of denosumab is reserved for cases with high surgical morbidity and for restricted time (Deventer et al., 2022).

In summary, the association between GCTB and a previous polypoid mass is exceptionally low and its occurrence extremely rare. In our patient, the first lesion occurred 4 years previously, with no signs of malignancy or complications, such as metastasis or spread, and only a single incisional biopsy was performed. The second lesion (i.e., GCTB) appeared as a silent event, gradually leading to the development of a slow-growing lesion that was difficult to diagnose until it externalized through the right nasal cavity and was perceived by the patient. Although these conditions may occur coincidentally rather than causally, we had to consider the possibility that these two entities were associated in our patient, and we acknowledge the relationship between activity of the remaining polypoid tissue in the nasal cavity and GCTB in all maxillary sinuses. We do not have supportive evidence to conclude that the first lesion became a GCTB; as such, more control studies are needed.

An interesting case described by Lentini et al. shows a rare case of Giant Cell of the Skin considered the soft tissue version of the GCTB. In their study, the marker CD68 was diffusely positive in the multinucleated cells and only focally positive in the mononuclear cells, positivity for Vimentina and negative for Ck AE1/AE3, contrasting our case report in the first biopsy. (Lentini et al., 2010). To the best of our knowledge, only one report in the literature has described a case of both GCTB and polypoid tissue that developed in the same location and in the head and neck region. Thus, we suggest a presumptive diagnosis of GCTB and polypoid tissue using computed tomography, NMR imaging, histopathology, immunohistochemistry, blood complementary testing, bone scintigraphy, and angiography, depending on the location, aggressiveness, and size of the lesion. Because the patient was located in another city and had limited financial resources, we were not able to investigate, in detail, the possible association of injuries. In addition, the public hospital where clinical care was administered lacked the resources to offer all of these tests.

5. Conclusion

The association between lesions occurring in the same location requires further and control studies, we hope that this article will help future research to explain a possible new case implicated in a new model of clinical, microscopic, and genetic disorders. Thus, masses originating from chronic inflammatory tissue may have the potential to transform into GCTB?

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