

## CASE REPORT

# Nodular fasciitis on the zygomatic region: immunohistochemical analysis and literature review

## Fascitis nodular en la región cigomática: análisis inmunohistoquímico y revisión de la literatura

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#### ABSTRACT

**Background:** Nodular Fasciitis (NF) is characterized as a benign, fast-growing lesion with proliferation of fibroblasts and myofibroblasts. The use of immunohistochemistry is important for the diagnostic definition and if its findings are not clear, the differential diagnosis will be challenging, even more when the clinical findings do not correspond with the histopathological characteristics.

**Objective:** Here, we reported a case of dermal Nodular Fasciitis affecting zygomatic region of a 64 years old male who complained of swelling in the right side of the face for 3 months, which appeared after an ox-horn trauma.

**Literature review:** We reviewed the literature for all Nodular Fasciitis cases in the zygomatic region. Furthermore, we discussed the relationship of trauma as an etiological factor, main differential diagnoses and immunohistochemical markers for Nodular Fasciitis.

**Case report:** Incisional biopsy was done which revealed benign neoplasm of mesenchymal origin characterized by the fusocellular proliferation. Immunohistochemistry revealed positivity for VIM and SMA, being negative for S-100, CKs, CD34, and p53. The Ki-67 index was low. Due to the clinical, histopathological and immunohistochemical findings, the diagnosis of dermal NF was established.

**Conclusion:** This case consists of Nodular Fasciitis, which must be microscopically differentiated from dermatofibroma, solitary fibrous tumor, low-grade myofibroblastic sarcoma and atypical fibroxanthoma. Immunohistochemistry should always be performed to elucidate the nature of tumor cells and thus contribute to the correct diagnosis and treatment. Nodular Fasciitis appears to be uncommon in the zygomatic region.

#### KEYWORDS

Nodular fasciitis; zygomatic; immunohistochemical; literature review.

#### RESUMO

**Introdução:** A Fasciíte Nodular (FN) é caracterizada como uma lesão benigna, de crescimento rápido, com proliferação de fibroblastos e miofibroblastos. O uso da imunoistoquímica é importante para a definição diagnóstica e se seus achados não forem claros, o diagnóstico diferencial será desafiador, ainda mais quando os achados clínicos não corresponderem às características histopatológicas.

**Objetivo:** Relatar um caso de Fasciíte Nodular dérmica acometendo a região zigomática de um homem de 64 anos que se queixava de inchaço no lado direito da face há 3 meses, que surgiu após trauma ocasionado por chifre de boi.

**Revisão da literatura:** A literatura foi revisada para todos os casos de Fasciíte Nodular na região zigomática. Além disso, discutiu-se a relação do trauma como fator etiológico, principais diagnósticos diferenciais e marcadores imunoistoquímicos para Fasciíte Nodular.

**Relato de caso:** Foi realizada biópsia incisional que revelou neoplasia benigna de origem mesenquimal caracterizada pela proliferação fusocelular. A imunoistoquímica revelou positividade para VIM e AML, sendo negativa para S-100, CKs, CD34 e p53. O índice Ki-67 foi baixo. Devido aos achados clínicos, histopatológicos e imunoistoquímicos, foi estabelecido o diagnóstico de Fasciíte Nodular dérmica.

**Conclusão:** Este caso consiste em Fasciíte Nodular, que deve ser diferenciada microscopicamente de dermatofibroma, tumor fibroso solitário, sarcoma miofibroblástico de baixo grau e fibroxantoma atípico. A imunoistoquímica deve sempre ser realizada para elucidar a natureza das células tumorais e assim contribuir para o correto diagnóstico e tratamento. A Fasciíte Nodular parece ser incomum na região zigomática.

#### PALAVRAS CHAVE

Fasciíte nodular; zigomático; imunoistoquímica; revisão da literatura.

## INTRODUCTION

Nodular Fasciitis (NF) was first described by Konwaler et al., in 1955<sup>1</sup>, and is characterized as a benign, fast-growing lesion with proliferation of fibroblasts and myofibroblasts. The use of immunohistochemistry is important for the diagnostic definition and if its findings are not clear, the differential diagnosis will be challenging, even more when the clinical and histological characteristics do not correspond. Therefore, NF is often misdiagnosed as soft tissue sarcoma.<sup>2</sup>

NF usually presents as a solitary mass measuring 1 to 3 cm, and there may be pain.<sup>3</sup> The most common locations are the upper extremities, 39% to 54% and the trunk, 15% to 20%,<sup>4</sup> but it may also appear in the forearm region and on the chest wall.<sup>5</sup> NF is rare in the head and neck region, with 7 to 20% of cases involving the intra-oral region,<sup>6</sup> including buccal mucosa,<sup>7</sup> buccal floor and tongue.<sup>8</sup>

On the face, extraorally, there are reports of NF affecting, ramus of the mandible,<sup>9</sup> masseter muscle and cheek.<sup>10</sup> The first case of dermal NF was described in 1990 by Goodlad and Fletcher.<sup>11</sup> To the best of our knowledge, only 14 cases of NF in the zygomatic region have been reported in the literature,<sup>4,12-23</sup> and no review of current literature on NF cases in the zygomatic region has been performed. The last specific review of cases in the zygomatic region was carried out in 2002, by Acocella et al.<sup>13</sup> and new cases have been published so far.

Thus, the aim of this study is to report an unusual case of dermal NF in the zygomatic region, in a 64-year-old male, with emphasis on differential histopathological diagnoses and the importance of immunohistochemistry to establish a correct diagnosis. In addition, we perform a literature review of NF cases in the zygomatic region.



**Figure 1.** Clinical feature showing swelling on the right side of the face. B, surgical excision of the lesion. C, immediate postoperative period. D, clinical feature after 12 months of follow-up, showing normal healing and no signs of recurrence.

A 64 years old male, melanoderm, farmer, from Sabinópolis city, Minas Gerais State, Brazil, complaining of a painful swelling in the right face for 3 months, which appeared after ox-horn trauma. He reported extraction teeth 14 and 15, with the use of antibiotics and anti-inflammatory, but no improvement of the lesion. The lesion kept growing in size with the presence of throbbing pain. The patient had no systemic diseases.

### Physical examination

On extra-oral examination it was observed a nodular lesion, normal color, smooth surface, sessile, well delimited, fibroelastic and measuring 4.5 x 4.0 x 3,0 cm (Figure 1A). The diagnostic hypotheses were neurofibroma, schwannoma and leiomyoma.

### Radiographic examination

X-Ray was normal excluding bone fracture (Figure 2).

### Biopsy and histopathologic analysis

Incisional biopsy was done which revealed benign neoplasm of mesenchymal origin characterized by the fusocellular proliferation. Based on this histopathological findings with the appearance of a benign neoplasia, the lesion was completely removed under local anesthesia, as

a form of treatment for the present lesion (Figure 1 B and C). Macroscopically the fragments of the lesion presented brownish with irregular shape and soft consistency (Figure 3A).

Histopathological examination showed a well circumscribed, encapsulated spindle cell lesion with hyaline and mixomatous areas. The cells were arranged in irregular bundles and fascicles along, and appeared to be immature myofibroblasts and fibroblasts (Figure 3 B and C).

Immunohistochemistry revealed positivity for vimentin (VIM) and smooth muscle actin (SMA), being negative for S-100, CKs, CD34, and p53. The Ki-67 index was low (Figure 4). Due to the clinical, histopathological and immunohistochemical findings, the diagnosis of nodular fasciitis was established. Post-operative was uneventful, and after 12 months of follow-up there were no signs of relapse (Figure 1D).

### Ethical approval

The present study was approved by the Research Ethics Committee of the Institution under protocol number: 2.934.465 and is in accordance with the Helsinki Declaration of 1964.

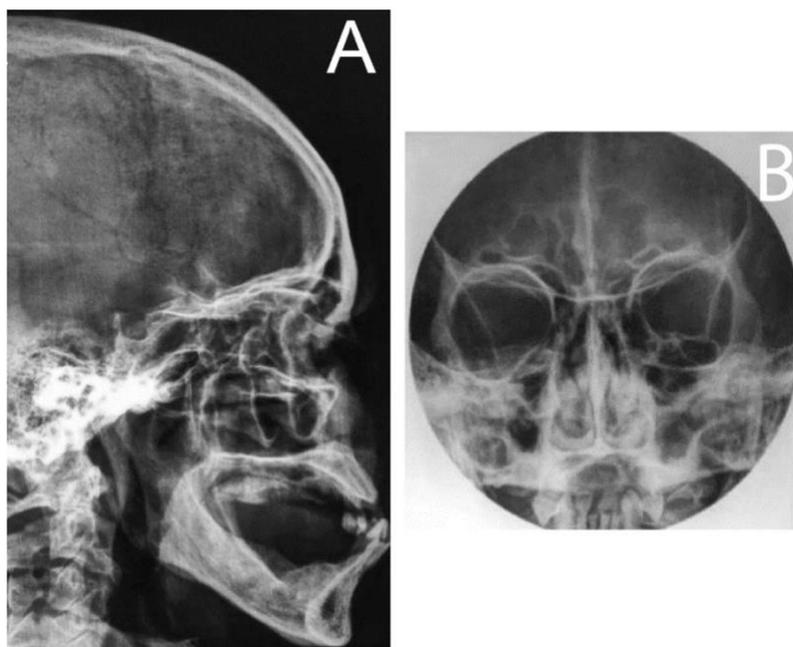


Figure 2. A and B, Lateral radiographic image of the face and Waters X-ray showing the absence of bone involvement by the lesion, respectively.

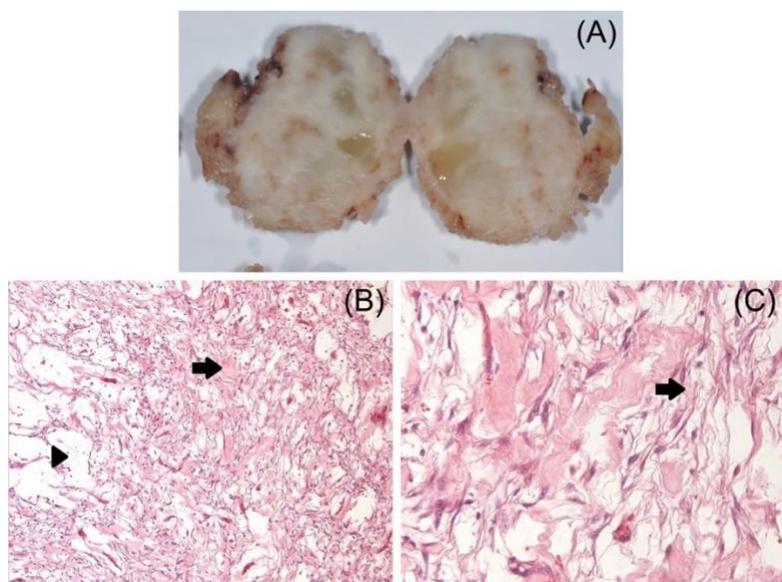


Figure 3. A, Macroscopic feature, showing whitish tissue with yellow-transparent areas. B, microscopic image evidencing a large proliferation of spindle cells with deposition of extracellular matrix rich in collagen fibers, with hyaline (arrow) and myxomatous areas (arrowhead) (Hematoxylin & Eosin – [H&E]; x100). C, large proliferation of spindle cells arranged in bundles and irregular fascicles (arrow), with fibroblast and immature myofibroblast characteristics (H&E; x400).

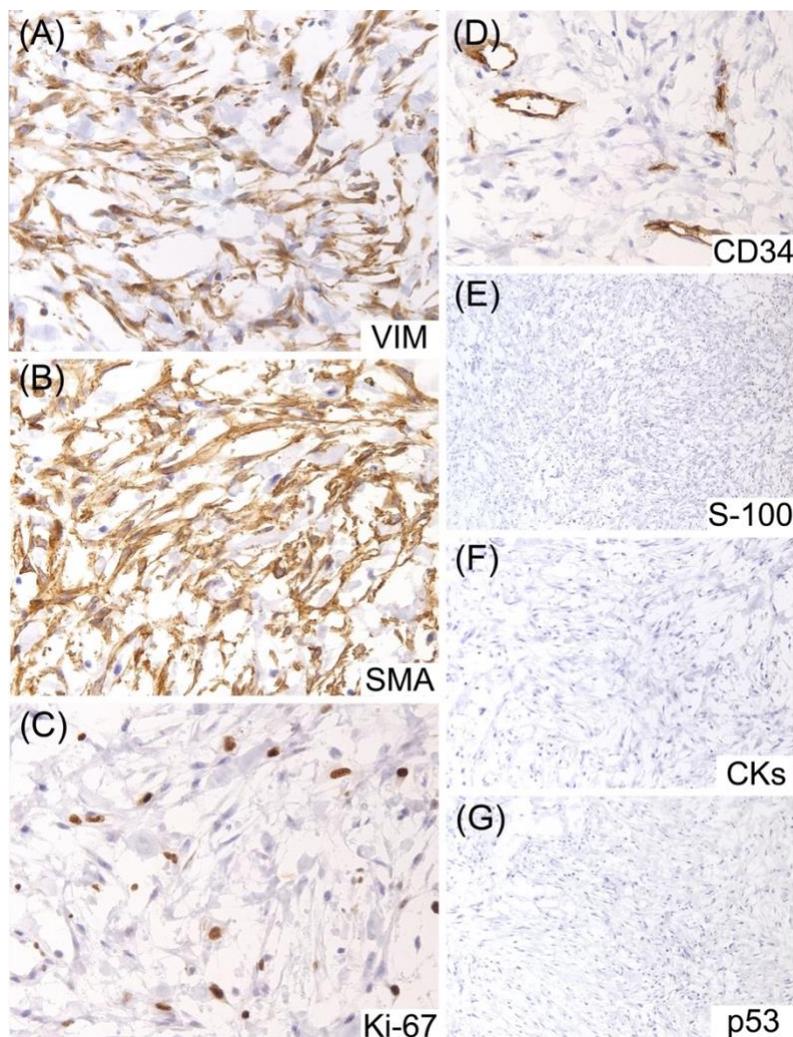


Figure 4. Immunohistochemical findings. A, strong positivity was found in spindle cells for VIM (x400). B, spindle cells showed high positivity for SMA (x400). C, Ki-67 marked the spindle cells, but in low quantity (x400). D, E, F and G, CD34, S-100 protein, CKs and p53 were negative on the spindle cells, respectively (D: x400; E and F: x200; G: x100).

**Table 1:** Clinicopathological features of the cases published of nodular fasciitis affecting the zygomatic region.

Authors	Country	Age (years)/gender	Clinical features	Laterality	Evolution time	Size (cm)	Trauma	Clinical diagnosis	Final diagnosis	Tissue plane	Immunohistochemical	Treatment	Regression after biopsy/time (Y/N)	Follow-up
1- Yoskovitch et al., 1998	Canada	39F	Left-sided painless cheek mass over the zygoma	Left	7 moths	5.0 x 8.0	Yes	NR	NF	NR	VIM+ Ck, S-100 protein, HMB-45, HHHF35, desmin-	Resection	No	NR
2-Acocella et al., 2002	Italy	12F	Swelling of the zygomatic region	NR	NR	1.5	Yes	NR	NF	NR	NR	Surgical excision	No	NR
3-Kang et al., 2002	Korea	41F	Firm, asymptomatic, pale erythematous and slightly elevated papule on the right cheek	Right	NR	0.5	No	NR	NF	NR	SMA and VIM+ Desmin, S-100 protein and factor XIIIa -	Surgical excision	No	24 months, no recurrence
4-Kim et al., 2005	Korea	18F	Rapidly growing cheek mass	Left	3 months	1.8	No	NR	NF	Dermal	NR	Surgical excision	No	NR
5- Kim et al., 2005		35M	Cheek mass	NR	1 months	1.5	No	NR	NF	NR	NR	Surgical excision	No	NR
6-Almeida et al., 2007	Spain	39F	Mass that had been growing rapidly in the right zygomatic area	Right	2 months	1.5	No	Fibroma, Leiomyoma, Sarcoma	NF	Dermal	NR	Surgical excision	No	24 months, no recurrence
7-Vyas et al., 2008	Canada	60M	Painless mass over the area of the right zygoma	Right	NR	2.0 x 1.3	No	NR	NF	Dermal	NR	Resection	No	3 months, no recurrence
8- Yanagisawa and Okada, 2008	Japan	27F	Well-circumscribed, firm, nontender mass in the soft tissues of the cheek. The mass was fixed to the zygoma	Right	6 months	3	No	NR	NF	Dermal	SMA and VIM+ S-100 protein and CD34-	Spontaneous regression	Yes, 1 month	24 months, no recurrence

<b>9-Souza e Souza et al., 2013</b>	Brazil	24F	Nodule on the right zygomatic region	Right	3 months	1	No	Epidermoid cyst, trichilemmal cyst and pilomatixoma	NF	Dermal	HHF35, SMA, Ki-67 + CD34, desmin -	Excisional biopsy	No	NR
<b>10-Oh et al., 2015</b>	Korea	58M	Coin sized skin colored deep seated nodule	Right	3 weeks	NR	No	NR	NF	Dermal	SMA + Desmin, Ck, CD34, S-100 protein, MART-1 -	Surgical excision	Yes	3 months, recurrence
<b>11-Shibata et al., 2016</b>	Japan	30M	Progressively enlarging subcutaneous nodule on the left cheek	Left	2 months	3.0	Yes	NR	NF	Dermal	VIM and $\alpha$ -SMA + Desmin, S-100 protein and CD34 -	Surgical excision	No	12 months, no recurrence
<b>12-Kumar, 2017</b>	India	10M	Small painless progressively enlarging swelling over right zygoma	Right	2 months	1.5 x 1.5	No	Osteoma, spindle cell neoplasm probably neural and fibrohistiocytic lesion	NF	Dermal	NR	Surgical excision	No	3 months, no recurrence
<b>13-Li et al., 2017</b>	China	12F	Progressively enlarging subcutaneous nodule on her left cheek	Left	20 days	2.0	No	Atypical conjunctive intraepithelial neoplasia and fibrous histiocytoma	NF	Dermal	NR	Surgical excision	No	12 months, no recurrence
<b>14-Xu et al., 2017</b>	Singapore	36M	Firm, well-circumscribed nodule over the left zygoma	Left	3 months	2.0	No	Low-grade mesenchymal neoplasm	NF	Dermal	S-100 protein and CD34 -	Surgical excision	No	24 months, no recurrence
<b>Present case 15-Gonçalves et al., 2021</b>	Brazil	64M	Painful swelling in the right face	Right	3 months	4.5 x 4.0	Yes	Neurofibroma, schwannoma and leiomyoma	NF	Dermal	VIM, SMA and Ki-67 + S-100 protein, CKs, CD34 and p53 -	Surgical excision	No	12 months, no recurrence

NR: not reported; F: female; M: male; NF: Nodular Fasciitis

## Discussion and literature review

### Search strategy

A review of the literature was conducted on the information collected from the Medline database via PubMed (<https://pubmed.ncbi.nlm.nih.gov>) and ScienceDirect (<https://www.sciencedirect.com>) up to sept 2021, with cross-referencing using the terms “nodular fasciitis and zygoma”; “nodular fasciitis and zygomatic” and “nodular fasciitis and face”. The identified references were stored in the EndNote software (Thompson Reuters, New York, NY, USA). After excluding non-NF articles in the zygomatic region, the search resulted in a total of 13 articles, with a total of 14 cases diagnosed as NF (Table 1). The references of the articles included were checked to prevent any article from not being included. The cases were published between the years 1998 to 2017. Regarding the location of the articles included, in Brazil,<sup>18</sup> Italy,<sup>13</sup> Spain,<sup>16</sup> India,<sup>21</sup> Singapore<sup>23</sup> and China,<sup>22</sup> one article from each country was found. Furthermore, in Canada,<sup>4,12</sup> and Japan,<sup>17</sup> two studies were included and in Korea three studies.<sup>14,15,19</sup>

The present study reports a rare lesion that presents as a benign tumor, but it may exhibit histopathological features, which can be mistaken for malignancy.<sup>1</sup> Thus, given the immunohistochemical findings, the diagnosis of nodular fasciitis (NF) was defined. It is characterized as a benign, fast-growing lesion with large proliferation of fibroblasts and myofibroblasts, with mitotic activity and histopathological pattern similar to other various oral cavity and facial lesions, such as sarcoma.<sup>24</sup>

The etiological factor is still unknown, however tissue trauma is pointed out as one of the etiologies, being reported in 10 to 15% of the cases,<sup>24</sup> which is in agreement with the present case, since an injury caused by a bull horn was a factor associated with the onset of the lesion. The etiology is still being investigated, and a study by Erickson-Johnson *et al.* showed that NF may be related to the positive regulation of the USP6 (ubiquitin-specific protease 6) transcript along with the fusion of the MYH9 (myosin heavy chain 9).<sup>25</sup> USP6 is an ubiquitin-specific protease, which is related to cellular processes involved in tumor oncogenesis. These findings reinforce the discussion among some authors that NF is a neoplastic growth and not a reactive inflammatory lesion.<sup>26</sup> Furthermore, due to its limited nature NF can be the first self-limited human lesion related to recurrent somatic gene fusion.<sup>25</sup>

The clinical feature of NF described in the literature as a

well-circumscribed solitary mass is similar to the clinical presentation of the current case.<sup>1</sup> Even with the pattern of lesion appearance in patients between the 3rd and 5th decades of life, as it is commonly reported in the literature NF can develop in people over 60 years of age, as showed in the present case.

According to the tissue plane involved NF is classified as: subcutaneous, intramuscular and fascial. The subcutaneous/dermal variant is the most common and presents as a subcutaneous and solitary nodule, in which the characteristics agree with the clinical findings presented in this study.<sup>9</sup> As described in this case, the diagnosis of NF is quite difficult and its histopathological characteristics are similar to other tumors of the oral cavity, so the use of imaging exams, contribute in part to know the extent, location and if there is bone involvement of the lesion, which favors the elaboration of the differential diagnosis. In the present case, a chest X-Ray was requested to discard any fracture that could have occurred due to the trauma caused by the bull horn injury and also to see whether the lesion had involved the bone or not. CT scan or MRI are very useful to support the diagnosis,<sup>27</sup> but we do not request these exams because they are expensive and the patient could not pay for them.

The average age of the cases found in the literature review was 31.5 years, with 7 (58.3%) of the cases on the right side of the face and an average of 3 months approximately of evolution of the lesion before diagnosis. In addition, only three others (21.4%) reported that trauma was associated with the appearance of the lesion, similar to the present case.<sup>12,13,20</sup> Thus, in cases in the zygomatic region, trauma does not seem to be associated with the appearance of NF. Clinically the most of the cases the lesion presents as a mass or nodule. The most common tissue plane was subcutaneous/dermal (n=10, 100%). Just over half of the studies (53.3%) reported the use of immunohistochemistry for diagnostic confirmation, including the present case. Surgery was most common treatment to NF, and only two cases (14.3 %) <sup>17,19</sup> there was spontaneous regression of the lesion after incisional biopsy, as reported by De Carli.<sup>6</sup> Only one study reported the recurrence of the lesion.<sup>19</sup>

In a literature review carried out by Xu *et al.* in 2017,<sup>23</sup> they found only three cases of NF in the zygomatic region. In our review, we show 14 cases of NF in this region. This difference can be explained by the fact that the authors did not report which databases were used and if there was a search for articles in the reference lists. In addition, to the cases reported by Xu *et al.*, 2017,<sup>23</sup> nine more cases were found by the year 2017 and two new cases emerged after their publication. Some studies report that NF is common in the zygomatic region, but what we show in this literature

review is that there are few cases in this region as well as in the facial region, when compared to the oral cavity, mainly in the buccal mucosa.<sup>10, 23</sup>

Furthermore, we found that not all cases performed immunohistochemical analysis, being only 7 including the present case. Until 2010, five studies did not perform immunohistochemical analysis for diagnostic confirmation. After that year, in 2017, two other studies also did not use the immunohistochemistry technique (Table 1). Although immunohistochemistry is essential for confirming the diagnosis of FN, it is still a technique that not all study centers have access to, in addition to being expensive. The most used immunomarkers with positivity for FN included VIM, SMA,  $\alpha$ -SMA, HHF35, Ki-67, while the negative were S-100 protein, Desmin, CD34, MART-1, factor XIIIa, Cks and HMB-45.

The histopathological similarity of NF with myofibroblastic sarcoma, myofibroma, dermatofibroma, and atypical fibroxanthoma (AF) is a challenge for the pathologist when defining the diagnosis, mainly because of the risk of diagnosing NF as a myofibroblastic sarcoma. Therefore, ways of minimizing the incorrect diagnosis and thus contributing to a conservative treatment to the patient should be used. Immunohistochemical analysis is essential for the diagnosis of NF, since only histopathological findings may not be conclusive. Immunopositivity to HHF-35, SMA, VIM and low Ki-67 were described in the literature, while negative expression was found for CD34, CD31, CD99, B-cell lymphoma 2 (Bcl-2), STAT6, anaplastic lymphoma kinase (ALK), S-100, p53, desmin cytokeratin.<sup>6,7, 24</sup> Therefore, the positive expression for SMA, VIM, and negative for p53 and pan-CK AE1/AE3 serve as a basis for the exclusion of carcinomas in microscopic differential diagnosis. Low-grade myofibroblastic sarcoma (LGMS) considered in the differential diagnosis is more cellularized than the NF and also has long fascicles that infiltrate the muscles causing their destruction, besides showing positivity for the CD34, CD99 and high Ki-67, unlike NF.<sup>6,28</sup>

Myofibroma usually does not present inflammatory infiltrate and exhibit a hemangiopericytoma (HPC)-like vascular arrangement and biphasic pattern, which does not appear in the NF.<sup>29</sup> Another differential diagnosis includes solitary fibrous tumor (SFT), but the positive stain for CD99, Bcl-2 and CD34, as well as negativity for SMA excludes this.<sup>30</sup> Dermatofibroma presents underlying epidermal hyperplasia, along with hyperpigmentation of the basal layer and elongated inter papillary ridges that most often do not extend into the subcutaneous tissue. In addition, dermatofibroma is negative for SMA, while NF

is positive.<sup>31</sup> In relation to the AF, the positivity for CD68, CD10, and CD99, and negativity for SMA differentiates it from NF.<sup>32</sup>

A discussion has been raised by authors in which the genes USP6 and MYH9 are found when analyzed by fluorescence *in situ* hybridization (FISH) in cases of NF. Thus, FISH becomes a new tool in the diagnosis of NF.<sup>25,26</sup> Another study showed 86% sensitivity and 100% specificity for the rearrangement of the USP6 gene in the diagnosis of NF, which contributes to the elucidation of this genetic rearrangement at the onset of NF.<sup>33</sup> However, as these studies were carried out a limited number of cases further researches with a larger sample are needed to confirm whether the detection of USP6 gene rearrangement is useful in diagnosing NF.

The treatment of the NF is complete removal of the lesion under local anesthesia, as done in this case. Relapses are rare and occur due incomplete removal of the lesion or incorrect diagnosis.<sup>16</sup> In the literature, there are reports of partial regression of the lesion after incisional biopsy.<sup>6,17,19</sup> Taken together, these findings show that NF has a good prognosis.<sup>7</sup>

#### *Strengths and limitations*

This study aimed to review all the literature available so far related to NF in the zygomatic region, also reporting the immunohistochemical markers used for diagnostic confirmation in the cases. As this is a clinical case, the conclusions are specific to the case reported. Longitudinal and/or multicenter studies with representative samples are needed to elucidate the diagnosis, treatment and prognosis of the lesion.

## CONCLUSION

This case consists of nodular fasciitis, which must be microscopically differentiated from dermatofibroma, solitary fibrous tumor, low-grade myofibroblastic sarcoma and atypical fibroxanthoma. Immunohistochemistry should always be performed to elucidate the nature of tumor cells and thus contribute to the correct diagnosis and treatment. NF appears to be uncommon in the zygomatic region.

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### ETHICS APPROVAL

The present study was approved by the Research Ethics Committee of the Universidade Federal dos Vales do Jequitinhonha e Mucuri under protocol number: 2.934.465 and is in accordance with the Helsinki Declaration of 1964.

### DECLARATION OF CONFLICT OF INTEREST

The authors state that there are no conflicts of interest to report in connection with this article.

### SOURCES OF FUNDING

The authors of this study have no financial relationships relevant to this article to disclose.

### RIGHT TO PRIVACY AND INFORMED CONSENT

The authors have obtained the written informed consent of the patient or subject mentioned in the article. The corresponding author is in possession of this document.

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