1. Abstract

Solitary fibrous tumor (SFT) is an exceedingly rare mesenchymal neoplasia that may occur in various districts; extrameningeal instances in the head and neck districts are rarely reported. Owing to its tendency to growth and recurrence, various classifications have been proposed for solitary fibrous tumor, characterized as low-, intermediate-, or high-risk. A correct diagnosis differentiating SFT from more benign soft-tissue tumors is fundamental given its unpredictable behavior: this concerns local aggressiveness, potential to spread, and mainly recurrences, that may appear decades after the first presentation. A valuable tool for a correct diagnosis is the gene mutation NAB2-STAT6, soon deemed as pathognomonic for SFT. The mutation is observed in nearly all differentiated SFTs thanks to immunohistochemical techniques targeting STAT6: these yield intense staining with a nuclear pattern. STAT6-negative SFTs are rare and normally dedifferentiated, with only few exceptions. In the present work, we report an exceptional case of an intermediate-risk SFT characterized by rapid growth and short time-to-recurrence, but that tested negative to the characteristic STAT6 immunohistochemistry despite being well-differentiated upon histological studies.

2. Introduction

Solitary fibrous tumor (SFT) is an exceedingly rare mesenchymal neoplasia with a reported incidence rate <1 case/million people/year [1], originally known as hemangiopericytoma. In the 2013 WHO classification of soft tissue tumors, the SFT became a standalone type of mesenchymal tumors. The hemangiopericytoma is now regarded as a variant of it, at a cellular phenotypical level [2]. In 2015, Kao et al. characterized the SFT for its recurrent chromosomal alteration, presenting the NAB2–STAT6 fusion gene [3]. The 5th WHO tumors classification brought about a further SFT differentiation: the distinction between ‘benign’ or ‘malignant’ was abandoned in favor of risk-stratification models for a better prognostic characterization [5]. The SFT is now divided into benign (locally aggressive), intermediate-risk, rarely metastasizing, and high-risk [1]. The SFT carries a risk for metastatic spread ranging from 10-30% to 35-45% or higher, depending both on tumor features and on length of follow-up [5,8]: recurrences have been reported even after decades [1,8]. The pleura remains its most common localization, while SFTs of the head and neck are uncommon. A relevant distinction is that between meningeal and extrameningeal SFT [6]. We report a clinical case with SFT localization at level of the left cheek, in a middle-aged Filipino woman who referred to us for an initial SFT manifestation and its later recurrence.

3. Case Report

We report a case of SFT of the facial region, in a 68-year-old Filipino woman with hypertension and type 2 diabetes. She referred to our attention in 2019 for a mass in the left zygomatico-maxillary region; it was non-painful, non-tender upon palpation, non-mobile over the deep facial planes, but mobile over the superficial ones. An ultrasound (US) exam was performed, reporting a well-vascularized, hypoechoic, solid lesion with inner septa and an external capsule in the left maxillary region. The lesion presented diameters of 45x18 mm and appeared as well-limited, located between the subcutaneous tissue and the bony plane. A contrast-computed tomography (CT) scan of the maxillofacial region was performed, reporting an inhomogeneous solid mass (40x23x36 mm) deep in the left maxillary region, characterized by high post-contrastographic enhancement. Posteriorly, the mass contacted the anteri-
or wall of the left maxillary sinus, with bony wall wear, but no infiltration. The mass was richly vascularized by the homolateral internal maxillary artery, with no lateral cervical or mediastinal lymphadenopathies. The initial suspect was that of an arterio-venous malformation. To perform further diagnostic workups, the patient was admitted in the UOSD of maxillo-Facial Surgery at the San Giovanni Addolorata Hospital in Rome. Given the high vascularity of the mass, embolization of the left internal maxillary artery branches feeding the lesion was performed, with no peri- or intra-procedural complication.

The first surgical resection was then performed: through a minimally invasive, intraoral incision in the superior left vestibular fornix, the multi-lobulated mass was dissected from the periosteum; it was filled with a high-viscosity content and coagulated blood. A small area of wear was observed in the anterior wall of the left maxillary sinus. Histopathology reported a 40 mm-mass, greyish, with red discolored areas, and a friable texture. Necrosis and granulation tissue from the previous embolization were reported. Some fragments of proliferation with oval-to-spindle cells were present, with a storiform growth pattern, low mitotic index, and fine capillaries. It tested positive to CD34 and for bcl2; negative to CD31 and with a proliferative index (measured with Ki67) of 5%.

Owing to the necrosis from the previous embolization, a certainty of diagnosis was hindered. Therefore, a neoplastic lesion of the SFT-type could not be ruled out. A post-operative antibiotic, analgesic and corticosteroid therapy was administered, and the patients was discharged in good general and locoregional conditions.

She underwent regular follow-ups that ruled out disease persistence or recurrence. 2 years later, she came to our attention with what appeared to be a disease recurrence. The lesion, localized in the previous region, was again non-painful, non-tender, mobile over the superficial planes but not over the deep planes.

In a month – needed for diagnostic exams - the mass endured an exponential growth. A contrast-enhanced angio-MRI, compared to the CT scan, reported a slight enlargement of the known subcutaneous left maxillary lesion (42x37x26 mm compared with 40x23x36 mm). Posteriorly, the lesion touched the left maxillary sinus anterior wall, with resulting thinning, and the infraorbital foramen, too. On its postero-medial aspect, it contacted tributaries to the left ophthalmic vein (non-stenotic). Lateral and caudal to the formation, further venous formations were found. The neoformation appeared solid and highly vascularized, supplied by branches from the left internal maxillary artery. A new embolization of the vessels feeding the hypervascular mass was scheduled: through a femoral access and super-selective catheterization of left facial and left internal maxillary arteries, the feeding vessels were embolized. The procedure was complicated by a transitory ischemic attack (TIA) with transitory right hemiparesis on the 1st post-operative day; intensive care unit (ICU) admission was needed. An urgent CT scan was negative, but a brain magnetic resonance imaging (MRI) showed hyperacute scattered lesions on DWI sequences, in the left-brain occipital cortex, frontal subcortical white substance, and cortex of the central and post-central gyri. The patient had no sequelae. Once the patient had recovered and medical therapy had been established, a new contrast MRI was performed as follow-up: the transitory nature of the ischemia was confirmed (no new brain lesions upon DWI), while the known subcutaneous left maxillary lesion of 42x37x26mm remained constant in aspect and signal features. A second embolization was performed. Some feeders from the left ophthalmic artery and right ECA were spared owing to procedural risks. The following day the patient underwent surgical excision of the mass with safe resection margins through a left Weber-Ferguson approach. It had mixed vascular and jelly content. The histopathological exam reported a densely packed spindle cell proliferation with oval nuclei and elongated, slightly eosinophilic cytoplasm mixed with rounded-quadrangular cells in a storiform pattern, with a modestly vascular stroma. Proliferative index was about 5% (Ki67). Neoplastic cells were CD34+ and Bcl2+, and SMA-, desmin-, and ps100-. The morpho-histochemical findings were consistent with extra-pleuric solitary fibrous tumor. Interestingly, immunohistochemistry for the gene rearrangement NAB2-STAT6 did not yield significant results. A mitotic count was performed for the neoplasm to fit into the Demicco classification system. There were about 6 mitoses/square mm, hence the neoplasm was classified as a intermediate-risk SFT (Table 1). A further 5-month follow-up contrast MRI reported scarring and thickening along the surgical incision, but no signs of recurrent disease. The anterior wall of the left maxillary sinus appeared regular. One year later, the patient is doing well and presents no signs of recurrence.

Table 1: Risk factor and score refer to the Demicco risk stratification model (De Bernardi et al. 1,10)

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<th>Risk Factor</th>
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<th>Presented Case</th>
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<tr>
<td>Age</td>
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<tr>
<td>- &lt;55</td>
<td>0</td>
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<td>- &gt;=55</td>
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<td>Tumor size (cm):</td>
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<td>- &lt;5</td>
<td>0</td>
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<td>- 5 to 10</td>
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<td>- 10 to &lt;15</td>
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<td>- &gt;=15</td>
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<td>Mitoses/ mm²</td>
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4. Discussion

An extremely rare mesenchymal tumour, the SFT now also encompasses the former hemangiopericytoma [1,2].

Common SFT sites are the serosal membranes of pleura, peritoneum,... In about 1/5 of cases, it can occur in the head and neck regions, thus its distinction into meningeal and extracranial [2,11]. In the head and neck, extracranial SFTs tend to affect the sinonasal tract and oral cavity, with orbital cases reported. It is rather a unique occurrence for an SFT to primarily involve the superficial soft tissues (e.g., the dermis). Satomi reports 38 cases occurred in the cheek, characterising it as a rare occurrence in this subsite [10]. Künzel et al. reported a cheek SFT incidence, among the head and neck SFT, of about 15% of all SFTs [12]. Freiser reported between 12 and 15% in the head and neck SFTs, where the cheek represents about 2%, characterising it as a rare tumor [13]. Oral SFTs tend to locate beneath the oral mucosa, tongue, and lower lip [14]; one of the potential etiologies of the oral SFT might be previous trauma [15], since the buccal mucosa is the area most affected by local traumas [16]. SFTs in the sinonasal tract and orbit tend to cause obstructive symptoms (sinonasal obstruction, epiphora...), while tumors in the deep soft tissues of the cheek or neck tend to silently grow, even for long time periods if asymptomatic. Otherwise, they may present as visible masses or with paresthesia/pain if causing nerve impingement. A degree of bone resorption has been reported in extrathoracic SFT cases such as those in the head and neck district, where they can behave like mass-occupying lesions and compress nearby structures [14]. In the case we report, the patient experienced a visible deformity in her cheek together with a certain bone thinning in the anterior maxillary sinus wall; it completely healed once the mass was removed. The SFT lacks specific clinical features and manifestations; therefore, there is a wide range of soft tissue conditions and neoplasms to consider for an accurate differential diagnosis. To this regard, the affected site plays an important role: in superficial soft tissues of the head and neck district, neurofibromas, schwannoma, myofibroma, leiomyoma, and salivary gland neoplasms should be considered and ruled out [16].

When localized in the superficial soft tissues, SFTs tend to grow smaller, likely because of an earlier detection. Nevertheless, given the malignant potential of this entity and their unpredictable behavior, care must be taken in operating a correct differential diagnosis, ruling out more benign affections of the mesenchymal tissues such as dermatofibrosarcoma protuberos or benign histiocytoma [14,16]. To this regard, immunohistochemistry offers a valid tool integrating histopathological examination: a tumor of mesenchymal origin, the SFT can present in a range going from an abundance of stroma to a hypercellular aspect [15,17,18]. A ‘patternless pattern’ of its spindle cell component and ‘staghorn vessels’ - more common in hypervascularised SFTs – are characteristic histopathological findings [19]. While differentiated and dedifferentiated liposarcoma express MDM2 and CDK4, the SFT lacks them [20]. A further tool to better differentiate the SFT from other tumors, and especially from sarcomas and mesotheliomas, is immunohistochemistry (IHC). Tariq et al. show that the combination of CD34, CD99 and Bcl2 usually has a strong expression in 90% cases. But these are quite low in specificity [21].

Instead, IHC for the C-terminus of STAT6, used as a proxy for the gene rearrangement product of NAB2-STAT6, has given higher sensitivity and specificity, respectively as high as 98% and 85% [18,22,23]. Although the NAB2-STAT6 fusion gene has been reported in nearly all SFT cases, [1] some SFTs may lack its expression, with negative IHC results. Usually, these instances have been attributed to a higher genomic instability, proper of dedifferentiated SFT, that can lose the expression of the NAB2-STAT6 fusion protein [5,24]. Tariq et al. analysed a set of SFTs, with a 100% positivity for STAT6, concluding that the NAB2-STAT6 mutation can be considered as pathognomonic for SFT [21]. 98% cases (59 out of 60) of SFT from a 2018 report by Doyle et al. showed nuclear expression of STAT6, usually diffuse and intense. The one not staining for it showed histological features of malignancy [25]. Mohajeri et al. identified the fusion gene NAB2-STAT6 in 90% of the SFTs they analysed. The fusion gene NAB2-STAT6 per se has not been found in other neoplasms to date [25].

In our reported case, histopathological features were not suggestive of malignancy: necrosis in the first sample was deemed as caused by the previous embolization procedure; as a further proof, said feature of necrosis was not found upon imaging preceding the embolization. Nevertheless, the neoplasm did have aggressive features, expressed in its tendency to recur. According to the Demicco model [10], our case was characterised as intermediate-risk, owing to both patient and tumor features (see Table 1). The case here presented fits, in our opinion, among the rare instances of STAT6-dedifferentiated SFTs in which this property cannot be attributed to dedifferentiation. A similar case to ours is found in a study of 36 head and

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- Low | 0-2 points |
- Intermediate | 3-4 points |
- High | 5-6 points |
neck SFT by Kao et al.: they too report a conventional sinonasal SFT for which IHC for NAB2-STAT6 resulted negative [3]. On the other hand, the one present in the work by Doyle et al. [20] had its negativity to the marker attributed to its dedifferentiation.

We used the Demicco model since it is particularly recommended for extrameningeal sites, and is the most widely used to date, too [1]. Another noteworthy classification is the 5th WHO sarcomas classification, characterised by a set of predictive criteria for metastatic and recurrence potential of SFT. There is overlap with the Demicco classification, with the WHO criteria comprising a distinction between pulmonary SFTs (usually deemed as benign) respect to the more malignant-oriented extrapulmonary ones. In more, the WHO 2020 classification defines the SFT as benign, locally aggressive (rarely metastasizing), and malignant [1]. Also according to the 2020-WHO classification, our case did not represent an openly malignant SFT, since none of nuclear atypia, high mitotic rate/proliferation, or necrosis of the infiltrative margins were present [4]. The benign-intermediate behavior of our reported SFT can also be observed in its expressed potential for local recurrence, well-defined margins, and in a moderate degree of local aggressiveness, limited to bone wear. These features are compatible with other instances of head and neck SFTs. In a work by Cox et al., out of 153 head and neck SFTs, only 6.5% showed malignant features [26]. Malignant cases usually present increased cellularity, nuclear atypia and pleomorphism, a high number of mitoses, and necrosis; in more, they are reported to exhibit necrosis, ill-defined circumferences with infiltrative borders, and local invasion [18,21]. Given the delicate anatomic localisation, and the important vascularization highlighted by pre-operative diagnostic studies, we decided to treat the neoplasm with embolization followed by surgery. Not encountering particular complications, we decided to apply this same protocol to the recurred mass. The TIA the patient experienced was likely not dependent on the embolization itself: the affected regions in her left brain were independent of the embolised vessels. We regard it as rather a complication of her age and comorbidities (hypertension, type 2 diabetes). A similar treatment strategy was adopted by Rizzo et al. to treat a sinonasal SFT, who decided as well to embolise the mass before approaching it, owing to the potential feared risks [9]. Surgery is regarded as the mainstay for localised disease [5]. Therefore, after the first resection and histopathologic report (stating that a SFT could not be ruled out), we opted for a close surveillance. This in accordance with a growing body of literature, whereby also Shmuly et al report good results with surgery: in their series, no patient experienced recurrence (2-74 month-follow-up) and, since their cases were all non-aggressive, they recommend this strategy [16]. There is little evidence that adjuvant chemo/radiotherapy might be of use in cases of local, non-aggressive disease [16,27]. Instead, dedifferentiated disease seem more sensitive to chemotherapy [27] (Figures 1-3).

Since the SFT in our case was an intermediate-risk lesion located in the head and neck district, rich with important anatomical structures, we opted to follow the literature and limit treatment to en-bloc resection [11,16,27].

We advised that the patient follow a strict follow-up regimen to ensure an early, likely less invasive treatment of potential recurrences – should they appear. But she skipped important follow up appointments. When she referred again (2 years from the initial surgery), in 2021, the mass had recurred, with notable dimensions. SFT is radiosensitive [16]. Large retrospective studies report a significant benefit from surgery + adjuvant radiotherapy (RT): 22% of the patients in the series received adjuvant RT, and they had better local control. Nevertheless, overall survival was not impacted [5]. Radiosensitivity is exploited in borderline resectable SFTs, and in those with a malignant potential [16]. Further studies are needed to safely state whether RT and/or chemotherapy can improve the recurrence rate. Demicco et al. reported a large rate of recurrence: despite adjuvant therapy being administered to 15% of patients, 29% of total patients presented with recurrence at a median follow-up of 48 months [2]. Varies series report SFT recurrence rates even higher than 10 to 25%, occurring even decades after the original surgery [5]. Identified risk factors for recurrence are larger tumor size [2], previous recurrences, R1 or R2 surgical resection, tumor size greater than 10cm independently from the original site, and histopathologic malignant features: it is reported that both pleural and extrapleural SFTs larger than 10 cm recurred both locally and as distant metastases [28,29]. Regarding head and neck SFTs, Smith et al. assess their local recurrence as high as 40%, with mainly local recurrence and a median time-to-recurrence of 10 years, stressing the importance of long follow up periods [30]. According to Demicco et al, who report recurrences after 19 years from the first resection in their large series of 103 SFT patients [2], the inhomogeneity in literature regarding metastatic rates might be explained by the short follow-up of some studies. We agree with a growing body of literature [1,8] that a long follow up is needed, especially for SFTs manifesting histopathological features of malignancy.

Figure 1: patient's first surgery: intra-oral approach
5. Conclusion

We described a rare SFT case, peculiar both in its short time-to-recurrence after a R0 surgical resection, localisation in the head and neck district, and, mainly, for its atypical histopathological features. Although there is now consensus regarding the NAB2-STAT6 positivity as pathognomonic for the SFT, the immunohistochemistry (IHC) for this marker may be negative in rare instances. Our case is atypical since most of the NAB2-STAT6 negative SFTs thus reported are dedifferentiated, with only a couple exceptions known so far. Once proven that a STAT6-negative SFTs is not dedifferentiated, the doubt arises regarding the implications of negativity of expression of the fusion gene NAB2-STAT6. To this day, this anomaly in tumor genetics has not been linked to an increased aggressiveness or to an initial malignant transformation. Yet, the doubt may arise concerning this molecular alteration, so that further studies in this sense are interesting. Although the SFT is rare and even more so in its STAT6-negative variant, its aggressiveness and tendency to recur are worth the effort. Long follow-ups become not only important in improving patients’ quality of life, monitoring potential recurrences or metastases that might be tackled at initial stages; but also, an opportunity to study potential transformations in the micro- and macroscopic behaviour of the rare SFT.

References


17. Tariq MU, Din NU, Abdul-Ghafar J, Park YK. The many faces of solitary fibrous tumor: diversity of histological features, differential diagnosis and role of molecular studies and surrogate markers in avoiding misdiagnosis and predicting the behavior. Diagn Pathol. 2021; 16(1).


