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Case Report

Sinonasal teratocarcinosarcoma treated with surgery and proton beam therapy: clinical, histological aspects and differential diagnosis of a new case

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Summary
Sinonasal teratocarcinosarcoma is a rare aggressive malignant tumor with a primary setting involving the nasal cavity followed by the ethmoid sinus and maxillary sinus. It accounts for approximately 3% of all head and neck cancers and less than 1% of all tumors. Nasal obstruction, recurrent epistaxis and headache represent the typical clinical presentation. Imaging shows the presence of a mass in the nasal cavity. The treatment usually consists of surgery and adjuvant intensity modulated radiotherapy. The rarity and the variability of the histological features make its diagnosis particularly difficult.
In this paper, we report a case of sinonasal teratocarcinosarcoma in a 62-year-old male treated with a multidisciplinary approach. As an alternative to intensity modulated radiotherapy, we proposed proton beam therapy for the first time. The patient benefited from the new and personalized protocol that provided excellent results and few adverse effects. At 45 months follow-up there is no evidence of relapse and the patient is in good health.

Key words: teratocarcinosarcoma, paranasal sinus neoplasm, radiotherapy, proton therapy

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Conflict of interest
The Authors declare no conflict of interest.

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Introduction

Sinonasal teratocarcinosarcoma (SNTCS) is a malignant tumor with an aggressive behavior, a poor prognosis, a high risk of recurrence and poor survival [1]. It arises in the nasal cavity, involving the ethmoid sinus in half of the patients and the maxillary sinus in a quarter of patients. Primary settings in the nasopharynx and oral cavity have also been reported. Moreover, an intracranial extension is also possible given the aggressive nature of the disease. SNTCS is a rare malignancy with 127 cases reported in the literature [2-3]. It was first described in 1983 by Shanmugaratnam with the name of "carcinosarcoma". Only a year later Heffner and Hyams coined the term "teratocarcinosarcoma" [4] and from 2005 it is recognized as a distinct entity in the WHO Classification of Head and Neck Tumors [1,6], representing approximately 3% of all malignancies of the region and less than 1% of all cancers. Patients (7:1 male to female ratio) are generally middle-aged men with a mean age at diagnosis of 54.5 years [1]. The typical onset consists of nasal obstruction, recurrent epistaxis and headache. Neurological symptoms are rare and reported

only in case of intracranial extension. The etiopathogenesis is still unknown.
Histologically they are heterogeneous lesions characterized by cells of different embryonic derivation (ectodermal, mesodermal and endodermal), in multiple degrees of differentiation [4]. The most widely used therapeutic approach is a combination of surgery and adjuvant intensity modulated radiotherapy (IMRT), but there are no official guidelines or consensus [7]. As an alternative to IMRT, proton beam therapy (PBT) is nowadays used to treat several head and neck tumors. In this report, the use of PBT for the treatment of a stage 3 SNTCS is discussed. It represents the first application to the best of our knowledge.

Case report

In June 2017, a 62-year-old male came to the Emergency Unit of the San Paolo Hospital (Milan) reporting a 12 hours unstoppable right-sided epistaxis. The patient experienced recurrent episodes of sinusitis, epistaxis, nasal obstruction, cacosmia and headache in the last four months. The symptoms were progressive and refractory to medical therapy. The patient stopped smoking in January 2017 (history of 4 cigarettes/day for 20 years - 4 pack/year history). Physical examination and the routine blood tests were non-contributory. During ear, nose and throat (ENT) examination, nasal endoscopy was performed-which revealed a large mass in the right nasal cavity (Fig. 1A, 1B). A computed tomography (CT) scan with contrast showed that the mass completely obliterated the right nasal cavity and maxillary sinus, extending to the nasopharynx; the remain sinuses were uninvolved and no intracranial extension was identified (Fig. 1C). Endoscopic sinus surgery (ESS) with radical intent was performed. The intraoperative examination was

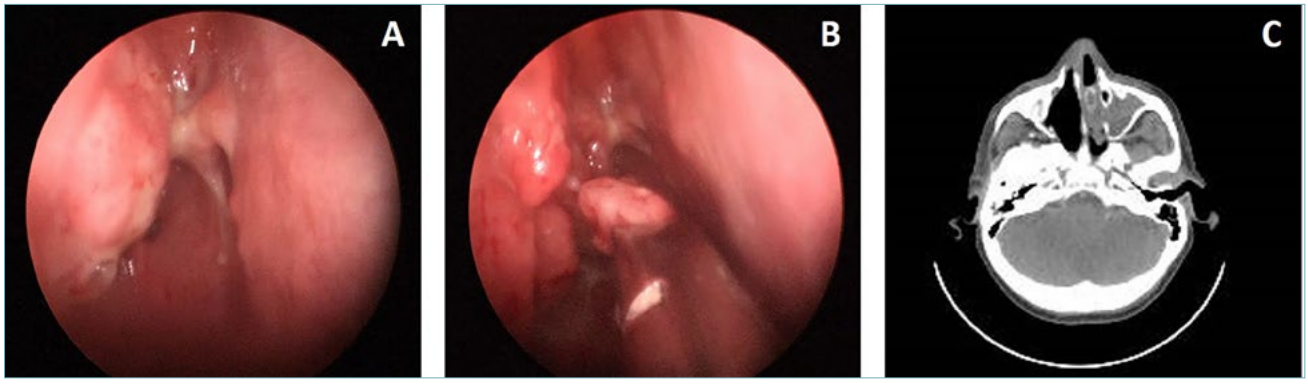

Figure 1. (A) Flexible fiber optic endoscopy shows the polypoidal mass in the right nasal cavity. (B) Biopsy performed during endoscopic sinus surgery (ESS). (C) Pre-surgical maxillo-facial CT shows a mass that completely obliterates the right nasal cavity, the ipsilateral maxillary sinus, and expands posteriorly toward the right nasopharynx.

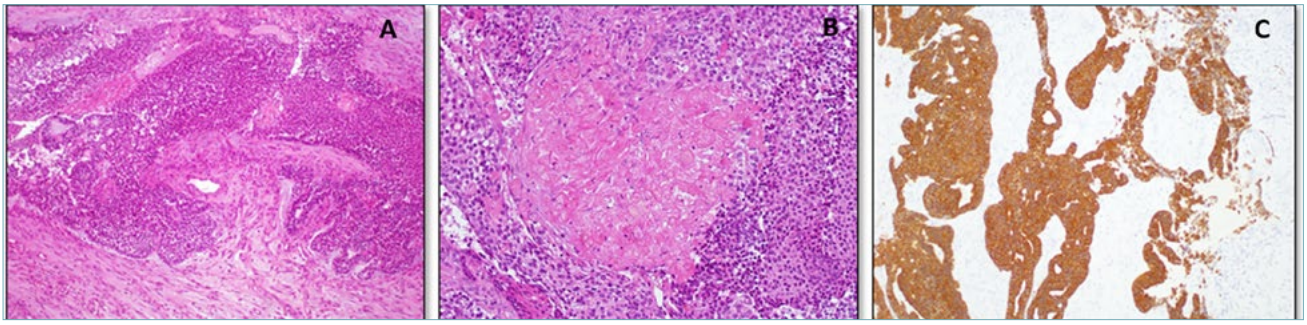

Figure 2. (A) Epithelial component, histology; small rounded elements partly organized in solid nests and peripheral palisade cells (H-E; 4x). (B) Epithelial component, histology; there are elements with different degrees of squamous differentiation and shadow cells (H-E; 10x). (C) Epithelial component, immunohistochemistry; it is positive for cytokeratins (AE1/AE3, Monoclonal mouse; DAKO; ready to use).

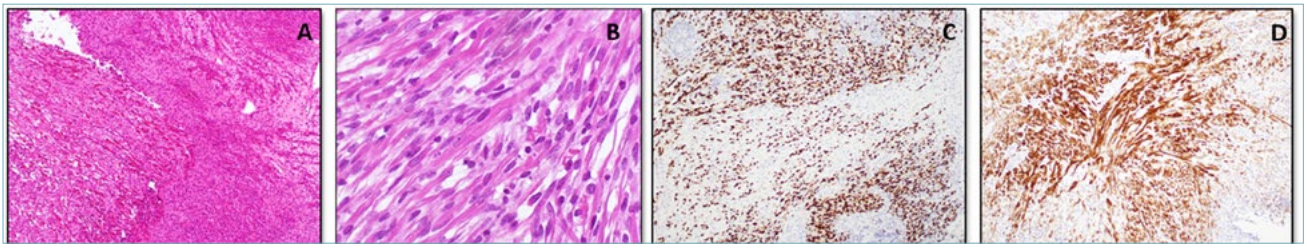

Figure 3. (A) Mesenchymal component, histology; it is for the most part made up of rhabdomyoblastic elements (H-E; 10x). (B) Mesenchymal component, histology; rhabdomyoblastic elements with the typical streak (H-E; 40x). (C) Mesenchymal component, immunohistochemistry; rhabdomyosarcoumatous component positive for myogenin (F5D, Monoclonal mouse; DAKO; ready to use). (D) Mesenchymal component, immunohistochemistry; rhabdomyosarcoumatous component positive for desmin (D33, Monoclonal mouse; DAKO; ready to use).

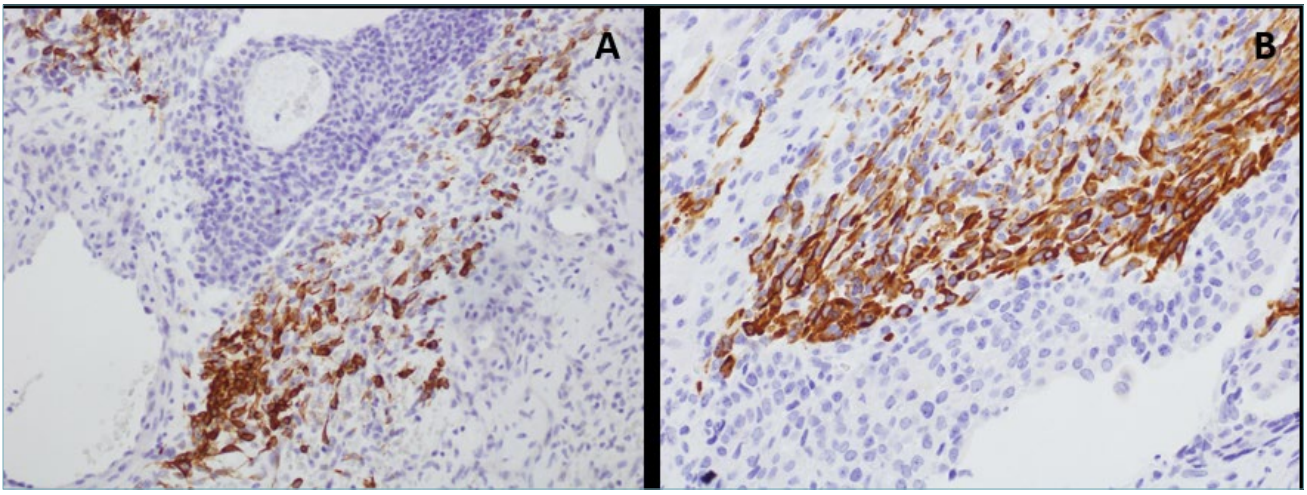

Figure 4. (A, B) Neuroectodermal component, immunohistochemistry; spindle elements crowded around the epithelial structures GFAP positive (6F2, Monoclonal mouse; DAKO).

inconclusive for the histological diagnosis, although margins were negative. The patient was discharged at day 1 in good health.

Histologic examination revealed a heterogeneous admixture of epithelial, mesenchymal and neuroectodermal components. The first varied from small rounded elements, partly organized in solid nests with peripheral palisade cells (Fig. 2A), sometimes with clear cytoplasm, to elements with squamous differentiation and shadow cells (Fig. 2B). There were micro-cystic and cystic formations, some of which with necrotic centers, and more rarely tubule/glandular structures, sometimes with ciliated cylindrical epithelium. The mesenchymal component was for the most part made up of rhabdomyoblastic elements (Fig. 3A) with the typical streak (Fig. 3B), with atypia from mild to moderate and some atypical mitosis. Finally, there were spindle elements of medium size which tended to crowd around the epithelial structures, mixed with fibro-mixoid areas. Necrosis and hemorrhage were present in about 30% of the sample. Neuroepithelium and elements of neuroectodermal origin were not clearly detectable based on hematoxylin and eosin staining.

Immunohistochemistry revealed positivity for myogenin (Fig. 3C) and desmin (Fig. 3D) in the rhabdomyosarcomatous component and pan-cytokeratin positivity in the epithelial component (Fig. 2C). The spindle elements crowded around the epithelial structures were GFAP positive (Fig. 4A, 4B).

The combination of morphology and immunohistochemistry made possible the final diagnosis of teratocarcinosarcoma.

Two months after resection, positron emission tomography (PET) examination revealed an accumulation of radiopharmaceutical at the level of the right nasal fos-

sa, confirmed by magnetic resonance imaging (MRI). A subsequent ENT evaluation revealed a polypoid lesion of the right posterior ethmoid sinus. Histologic examination confirmed a residual SNTCS. A multidisciplinary treatment approach was planned and the patient underwent 33 PBT sessions. Treatment was administered 5 days a week from January to March 2018 at Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia (Italy). The patient received 66 Gy in 2 Gy daily fractions and the radiation dose delivered to the adjacent healthy tissue did not exceed 5 Gy. In January 2019 (18 months after diagnosis), a follow-up PET examination was performed with no evidence of recurrence. In April 2020 (34 months after diagnosis), the patient underwent a head and neck MRI, which was negative for relapse or nodal metastases. During the treatment the patient reported loss of the right eyebrow and beard, actinic rhinitis and hyposmia (the latter only in the last two weeks of treatment). To date (45 months after diagnosis), the patient has only moderate post-actinic vestibulitis.

Discussion

SNTCS is an extremely rare malignant tumor mostly located in maxillary and ethmoid sinus (50% and 25% respectively) [1,8]. Orbit, oral cavity, pharynx and anterior cranial fossa are rare localizations, while bone erosion and extracranial extension are anecdotal, especially at onset [9]. Moreover, intracranial extension is also possible.

Macroscopically, these tumors present as bulky reddish masses. Histologically, epithelial, mesenchymal and neuroectodermal components include the teratoid component of the tumor [10]. The epithelial structures can vary from poorly differentiated cell nests to well differentiated squamous cells with formation of horny pearls and glands focally containing mucin. The “fetal-appearing” squamous epithelium is a common feature, consisting in squamous cells with clear cytoplasm. It has been described in the literature in about 50% [8] to 75% [5] of the tumors. The mesenchymal component can be composed of cartilage, bone, striated muscle and smooth muscle, usually with cytologic atypia and immaturity [10]. The neuroectodermal component can be organized into rosettes and pseudorosettes [9,12].

The rarity of the tumor and the microscopic variability make the diagnosis difficult and challenging. A combination of carcinosarcoma and teratoma are required [10] and immunohistochemistry is fundamental to support the diagnosis. The epithelial component shows positivity for pan-cytokeratins, the neuroectodermal elements show variable positivity for GFAP, S-100, NSE, CD99, chromogranin and synaptophysin and the mesenchymal component results positive for vimentin and/or myogenin and/or desmin [8]. SNTCS should be put in the differential diagnosis with multiple malignancies including poorly differentiated squamous carcinoma, sarcomas, malignant craniopharyngioma, small cell carcinoma and undifferentiated sinus carcinoma, from which it differs in the coexistence of carcinomatous, sarcomatoid and neuroectodermal elements. SNTCS for its typical undifferentiated round-shaped cells mimics the olfactory neuroblastoma; these two tumors have a similar neuroectodermal differentiation, but they can be distinguished by the evident epithelial differentiation and by the presence of neoplastic mesenchymal components that characterize SNTCS. Another possible differential diagnosis is with malignant teratoma, but it should be considered that teratomas are mainly found in the reproductive system and in other parts of the body (mediastinum, retroperitoneum), while the location of teratocarcinosarcoma is well-defined in the head and neck district. Furthermore, malignant teratoma lacks immature squamous cell nests (clear cell nests or blastic cells) and does not have carcinomatous features [12]. Carcinosarcoma is distinguished because this tumor consists of a single malignant epithelial component and a single malignant mesenchymal component [8]. Moreover, it is important to put in differential diagnosis lymphoma and melanoma, but the negativity for the specific tumor markers excludes these entities. Considering all these possible differential diagnoses, it is easy to understand how biopsy specimens of limited dimensions may represent a problem for the diagnosis, either for the insufficient representativeness of the sample and for insufficient material necessary for immunohistochemistry.

The most relevant review of SNTCS was published in 2014 by Misra and colleagues [1], who identified surgery and neoadjuvant IMRT as the most common treatment (survival rate of 56.5% and relapse rate of 26.1%). Among radiation treatments, PBT has a promising potential in disease control in patients with head and neck cancer, particularly sinonasal cancer [13]. PBT has fewer side effects and improves quality of life. Hence, its use has increased in recent years and it shows a potential superiority over classical photon therapy, reducing toxicity and side effects [13]. PBT is a type of external radiotherapy that produces a concentrated proton beam focused on a specific target [14]. The main characteristic of protons is the absence of an exit dose outside the target and a sharper lateral dose distribution due to the heavier mass of the protons. This distinguishes proton therapy from conventional photon therapy [13]. Several studies report on dose reduction to

non-target structures, preservation of normal tissues and potential improvement in tumor control in patients receiving proton beam therapy compared to patients receiving conventional radiotherapy [14-18]. However, proton therapy has some limitations including limited availability and costs (2-3 times higher than traditional radiotherapy) [19-25]. Due to the benefits of PBT and its efficacy on other sinonasal tumors [26-28], our group decided to propose it to the patient. More than 40 months after diagnosis, our patient is in good health, ESS and PBT have been well tolerated and there are no signs of recurrence or metastases.

Conclusions

SNTCS is an aggressive tumor often misdiagnosed due to its rarity, histologic complexity and variability. Recent studies demonstrate how a combined approach with surgery followed by radiotherapy and chemotherapy can improve the prognosis. Further studies are needed with a larger sample size for a better understanding of the best multidisciplinary management of the disease. It would be also interesting to investigate the positive outcomes that proton therapy can have when substituted to conventional radiation therapy, improving the survival rate and limiting the side effects of radiation in selected patients.

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