ORIGINAL PAPER

Sinonasal Leiomyosarcoma: Clinicopathological Analysis of Nine Cases with Emphasis on Common Association with Other Malignancies and Late Distant Metastasis

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Abstract

Sinonasal tract (SNT) leiomyosarcoma (LMS) is exceedingly rare with < 100 cases reported. Their relationship to retino-blastoma and other malignancies, along with previous irradiation has not been clarified. Routine and consultation cases were reviewed for histologically and immunohistochemically proven SNT LMS. The tumors were tested with antibodies against α-smooth muscle actin, desmin, h-caldesmon, HMB45, S100 protein, Rb1, MDM2, CDK4 and EBV (EBER-ISH). Nine tumors affecting 5 males and 4 females aged 26 to 77 years (median: 48 years) were identified in the maxillary sinus (n = 4), nasal cavity (n = 3) and combined SNT (n = 2). Three patients had previous irradiation (2 for retinoblastoma, 1 for fibrous dysplasia) and 1 patient had chemotherapy and stem cell transplantation for Hodgkin lymphoma. One patient had prostatic adenocarcinoma (prior) and rectal adenocarcinoma (post) to the LMS. All patients with follow-up developed either local recurrences and/or metastases, principally to lung (time to metastasis: 16–156 months, mean 62 months). Histologically, 6 tumors were conventional high-grade LMS, two had glycogen-rich clear cell (PEComa-like) morphology and one was spindle cell low-grade. The latter showed grade 2 in the recurrence and grade 3 in the lung metastases. Two cases showed dedifferentiation to anaplastic pleomorphic (inflammatory MFH-like) phenotype. Immunohistochemistry revealed diffuse expression of at least 2 smooth muscle markers in 8 and only actin in one case/s. All other markers were negative. RB1 loss was observed in 6/8 cases tested. Sinonasal tract leiomyosarcomas are rare aggressive sarcomas that frequently develop in a background of previous cancer therapy (4/9), most frequently irradiation. Their varied morphology underlines the wide differential diagnostic considerations. Long-term survival may be achieved with aggressive multimodal therapy.

Keywords Leiomyosarcoma · Nasal cavity · Maxillary sinus · Sarcoma · Muscle, smooth · Immunohistochemistry · Retinoblastoma

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Introduction

Leiomyosarcoma (LMS) is an aggressive mesenchymal neoplasm that shows smooth muscle differentiation by histological, immunophenotypic and ultrastructural examination [1]. LMSs are uncommon, comprising no more than 7% of all soft tissue sarcomas [1]. The main sites of origin are uterus, skin/soft tissue and retroperitoneum with only around 3% affecting the head and neck area [1].

Mesenchymal neoplasms of the sinonasal cavities are uncommon. They comprise < 5% of all tumors of the sinonasal tract. In a review of 256 mesenchymal tumors of the sinonasal and nasopharyngeal cavities by Fu and Perzin, smooth muscle neoplasms represented 3% of the total cohort [2]. In the same study, LMSs comprised 2.3% of all and 6% of malignant non-epithelial neoplasms [2]. Sinonasal tract

(SNT) LMSs are exceptionally rare with no more than 100 cases reported in the English literature, with most as single case reports [3–7]. Thus, only limited data is available on their morphological spectrum and other clinicopathological and prognostic characteristics. In this study we analyzed histologically proven SNT LMS identified in our routine and consultation files.

Materials and Methods

All tumors coded as sinonasal tract leiomyosarcomas were identified in our routine surgical pathology and consultation files. Histological slides were reviewed to verify diagnosis and immunohistochemistry was performed on 4-µm sections cut from paraffin blocks using a fully automated system (Benchmark XT, Ventana Medical Systems Inc, Tucson, Arizona, USA) using the following antibodies: desmin (clone D33, 1:250, Dako), α-smooth muscle actin (clone 1A4, 1:200, Dako), h-caldesmon (clone h-CD, 1:100, Dako), S100 protein (polyclonal, 1:2500, Dako), HMB-45 (clone HMB45, 1:50, Enzo), p53 (clone DO-7, 1:50, Dako), MDM2 (clone IF1, 1:50, CalBiochem), CDK4 (clone DCS-156, 1:100, Zytomed) and RB1 (1:200, BD Biosciences, Heidelberg, Germany). Epstein Barr virus (EBV) in-situ hybridization (EBER 1/2 probes, ZytoVision, Bremerhaven, Germany) was performed according to the manufacturer guidelines. Positive and negative controls were used throughout.

Results

General Clinical and Demographic Features

Nine patients with primary SNT LMS were identified (Table 1). One patient had a sinonasal metastasis from a primary soft tissue LMS (of the hand) diagnosed > 20 years ago with recurrent metastases at diverse sites over two decades. This patient (the only case with sinonasal metastasis from a soft tissue LMS in our records) was excluded from further analysis. In one of our institutions, there were 3 SNT LMSs (0.01%) out of 28,026 SNT specimens submitted in the period 2007–2017. During this same period, 6 SNT leiomyomas were encountered, thus suggesting benign leiomyomas are more common than LMSs. Finally, the 3 SNT LMSs represented 0.35% of all 861 LMSs from all body sites during the same period.

The nine primary SNT LMSs affected 5 males and 4 females aged 26 to 77 years (median 48 years, mean 49 years). Tumor affected the maxillary sinus (n = 4), nasal cavity (n = 3) and combined nasal cavity and paranasal sinuses (n = 2). Three patients had a history of previous

irradiation (2 for retinoblastoma and one for fibrous dysplasia). A fourth patient (the youngest in this series) had a history of chemotherapy and stem cell transplantation for Hodgkin lymphoma performed five years prior. The retinoblastomas were diagnosed at age 3 and 1.5 years, respectively. The interval between the retinoblastoma and/or irradiation and LMS diagnosis was 40 and 25 years, respectively. Of the two patients with retinoblastoma, one had bilateral disease with a positive family history indicating hereditary retinoblastoma syndrome. The other patient had unilateral disease and a negative family history. Her LMS was ipsilateral to the retinoblastoma and irradiation side. One patient (the oldest in this series) had prostatic adenocarcinoma at age 73, SNT LMS at age 77 and rectal adenocarcinoma at age 81. Notably, this patient developed multiple lung nodules, which proved after resection to represent an admixture of metastases from both his LMS as well as his rectal adenocarcinoma. Analysis of the mismatch repair proteins in this patient revealed intact expression making a hereditary nonpolyposis colorectal cancer (HNPCC) syndrome unlikely. A final patient had a history of endometrioid endometrial adenocarcinoma.

Follow-up was available for 8 patients, ranging from 6 months to 17 years. Two patients died of local disease complications (extension into brain from primary tumor or local recurrence) at 6 and 30 months. Local recurrence developed in four of eight patients at 16–28 months. In addition, distant metastases affected four of eight patients (all had lung metastases, while one also developed brain metastases). Metastases developed at 16, 20, 55 and 156 months. Thus, two developed local recurrence only, two developed distant metastases only and two patients had both. At last follow-up, three patients were alive without evidence of disease 6–17 years. Notably, two of the survivors had surgically resected lung metastases several years earlier. Only one patient was alive without metastases at last follow-up. Thus, all patients with follow-up developed either local recurrences and/or metastases, the latter primarily to lung between 16 and 156 months (mean 62 months).

Pathological Findings

Grossly, the tumors were described as fleshy with whorled whitish cut-surface, firm to soft, with variable regions of hemorrhagic necrosis (Fig. 1a). Histologically, all tumors showed cytological and architectural features of smooth muscle neoplasms with elongated, blunt-ended, vesicular nuclei and brightly eosinophilic fibrillary cytoplasm arranged into compact intersecting fascicles (Fig. 1b–d). Perinuclear vacuoles were characteristic. Six tumors were conventional high-grade neoplasms, showing brisk mitotic activity [defined as > 10 mitoses/10 high power fields (Fig. 1d)] and areas of tumor necrosis, two

Table 1 Clinicopathological features of sinonasal leiomyosarcomas (n = 9)

| No.	Age sex	Site	Treatment	Associated tumors	Previous irradiation or chemotherapy?	Family history	Follow up and outcome
1	77 M	Right nasal cavity + maxillary sinus	Excision and radiotherapy	Prostatic carcinoma at age 73 Sinonasal leiomyosarcoma at age 77 Rectal carcinoma at age 81	Anti-androgen therapy for prostate cancer	No	55 months later, there was resection of multiple lung metastases of both rectal cancer and leiomyosarcoma Currently, alive with disease at 88 months
2	48 F	Left nasal cavity + sinuses	Excision and adjuvant radiochemo-therapy	Tubulovillous rectal adenoma, 13 years later	No	No	Local recurrence middle turbinate (26 months) Two metastases to the right lower lung lobe (13 years) Alive with no evidence of disease at 17 years
3	43 F	Right nasal cavity	Excision and radiochemo-therapy	Retinoblastoma of right eye at age 3	Radiotherapy for retinoblastoma	No	At 16 months, imaging showed solitary lung metastasis, cerebral metastasis and local recurrence (not verified histologically) Lost to follow-up thereafter
4	61 M	Nasal cavity	Surgery	Not known	Not known	Not known	Not known
5	28 M	Maxillary sinus, infiltrating dura	Surgery	Not known	Not known	Not known	Multiple recurrences over 16 months, then lost to follow-up
6	26 F	Maxillary sinus	Radical maxillect-omy	Hodgkin Lymphoma (Stage IIIB in 3/2003) Allogenic stem cell transplantation after recurrent Hodgkin (2011) Bad GVHD	Chemotherapy then stem cell transplant in 2004	No	Lung metastases at 20 months, treated with surgery Alive without evidence of disease at 8.2 years
7	27 M	Maxillary sinus	Wide excision	Retinoblastoma (bilateral) at 18 months (bilateral blindness) Macrocytosis Intellectual disability with epilepsy/seizures	Yes: for retinoblastoma; 2 times: at initial and then at age 2 after second eye developed retinoblastoma	Mother had retinoblastoma and rhabdo-myo-sarcoma	Local recurrence at 2 years which resulted in brain invasion Dead of disease at 2.4 years
8	66 F	Nasal cavity	Wide excision	Grade 1, Stage 1A uterine endometrioid adenocarcinoma (1999)	No	No	Alive without evidence of disease at 6.6 years
9	66 M	Maxillary sinus	Wide excision	Polyostotic fibrous dysplasia	Yes: irradiation for fibrous dysplasia at a younger age	No	Brain extension resulted in death from disease at 0.5 years

M male, *F* female, *GVHD* graft-versus-host-disease
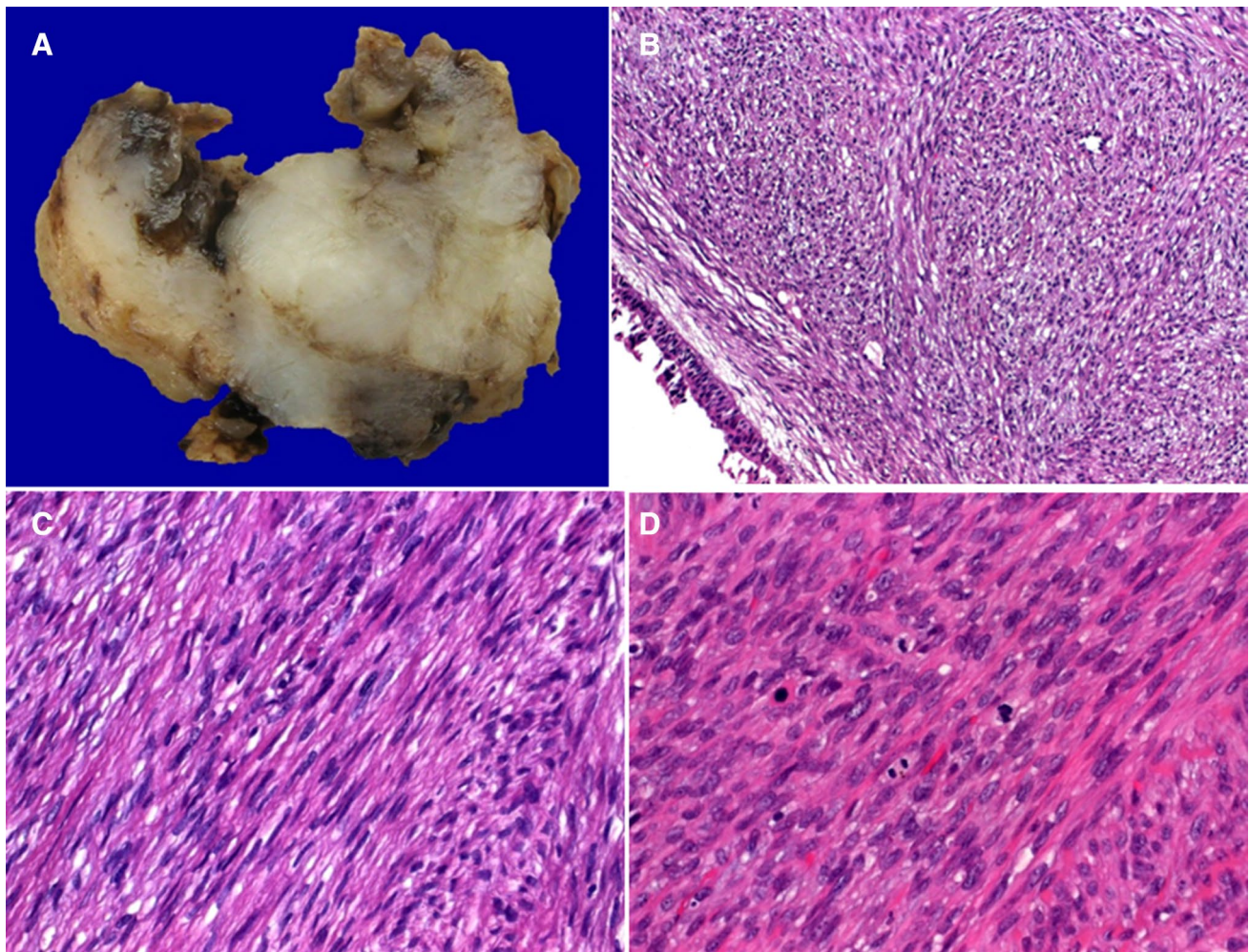
Fig. 1 Sinonasal leiomyosarcomas present as non-encapsulated irregular fleshy masses with areas of necrosis (**a**) covered by respiratory mucosa (**b**). They range from low-grade (**c**) to high-grade (**d**) with variable mitotic activity

tumors had variable epithelioid glycogen-rich clear cell (PEComa-like) morphology but with high-grade nuclear features (Fig. 2a–d) and one was spindled cell, but low-grade (Fig. 1c), showing only 2 mitoses/10 high power fields and lacking necrosis (Table 2). The latter showed grade 2 LMS in the recurrence and grade 3 LMS in the lung metastases. Two cases showed dedifferentiation with abrupt transition to anaplastic pleomorphic (inflammatory MFH-like; Fig. 2a, c) or epithelioid pleomorphic phenotype in the primary tumor or in the recurrence. Immunohistochemistry revealed diffuse expression of 2 or more smooth muscle markers in eight cases and only actin in one case (Fig. 3a, b). All other markers were negative. RB1 loss was observed in 6/8 cases (Fig. 3c).

Discussion

SNT LMSs are rare aggressive sarcomas that represent only 2–3% of non-epithelial tumors of the SNT and nasopharynx [2]. They frequently develop in a background of previous cancer therapy or irradiation for retinoblastoma [8–10], other malignancies such as lymphomas or even for benign conditions as exemplified by fibrous dysplasia in one of these cases. 4 of 9 cases in our current study fall into this group of LMS developing after previous cancer therapy applied to the general anatomic region.

A history of retinoblastoma was recorded in 24% of reported cases [8–10]. Moreover, a history of head and
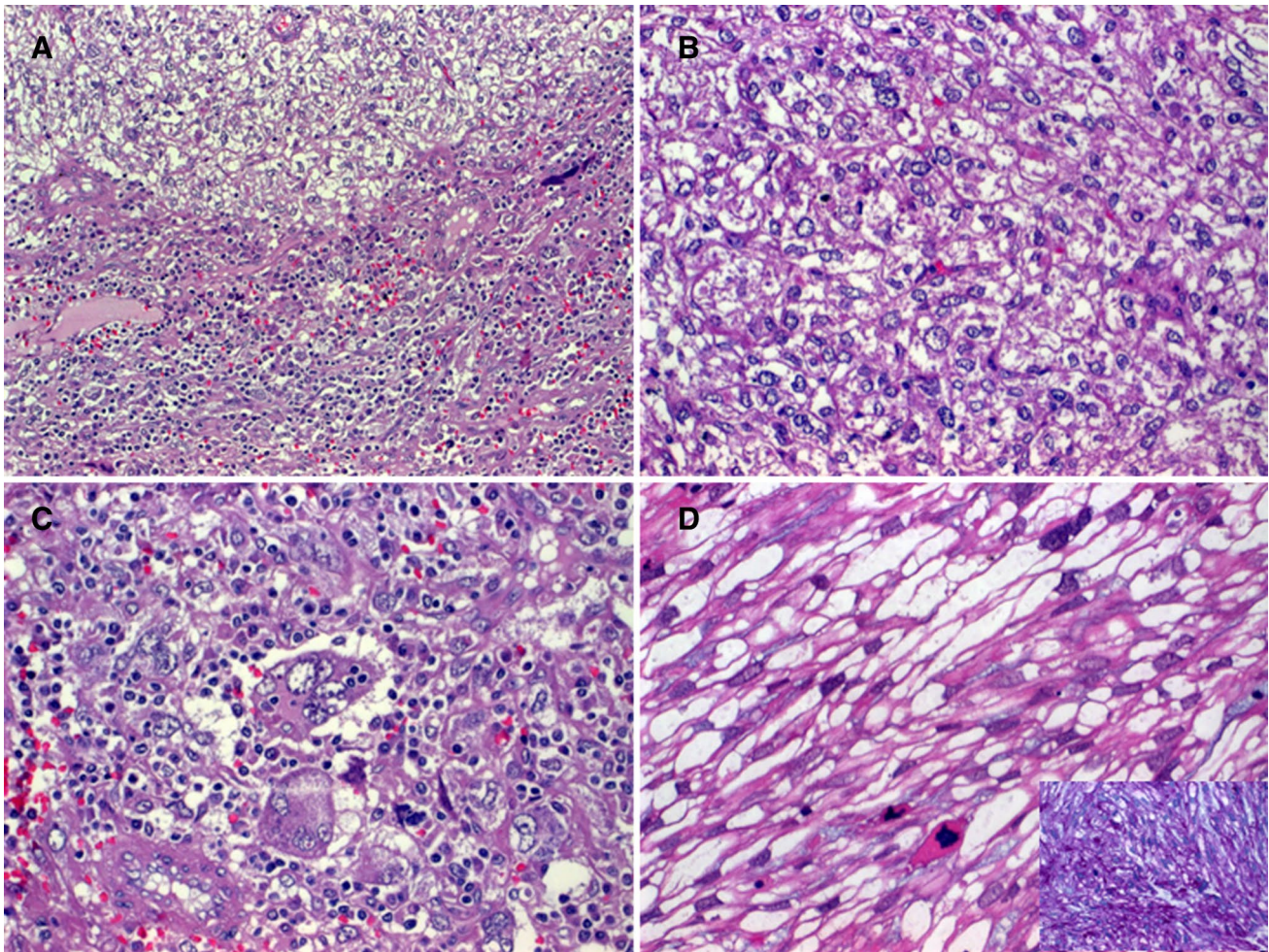
Fig. 2 **a** Transition from epithelioid clear cell (upper field in **a**; **b** high power of clear cell epithelioid areas) to inflammatory "MFH"-like pattern (lower field in **a**; **c** high power). **d** another case showed spindled glycogen-rich clear cells with high-grade features (inset: PAS)

neck irradiation and of systemic chemotherapy was recorded in 18/63 (28%) and 3/63 (4.8%) reviewed cases, respectively [6–10]. It is well known that second primary neoplasms occur more frequently in survivors of hereditary retinoblastoma (14%) than in those with presumably non-heritable retinoblastoma (1.8%) [8–10]. In one large study from the United Kingdom, LMS was the main malignancy in the hereditary subcohort followed by osteosarcoma and skin melanoma [9]. In that study, head and neck sarcomas were more frequent in the hereditary versus non-hereditary subgroups and within the hereditary subgroup, the head and neck involvement was more frequent than other body sites, suggesting a multifactorial or synergistic (combined) effect for the presence of germline *Rb1* deficiency and irradiation in the sarcomagenesis.

In contrast to earlier assumptions that SNT LMS have a lower rate of distant metastasis (8%), our series showed a distant metastasis rate of 50%. This discrepancy is likely a reflection of the extent and completeness of follow-up.

Distant metastases in our series occurred 16 months to 13 years (mean, 62 months) after diagnosis and therapy of the primary tumors and 2 of 4 cases developed metastases > 4.5 years after initial therapy, well beyond the median follow-up of 38 months in a review of 63 previously reported cases [6]. Accordingly, our series highlights the necessity for a careful and extended follow-up for patients with SNT LMS due to the high frequency of late distant metastases, developing as late as 13 years after primary treatment. We also observed a high local recurrence rate (4/8), with patient death due to local complications.

Another important finding highlighted by the current series, is the possibility of long-term survival in spite of metastatic disease. Thus, it seems justified or reasonable to consider surgery for oligometastatic disease. This feature seems to be unique from LMS of soft tissue and other organs, where disease progression is usually rapid and fatal after development of systemic metastases from high-grade tumors.

Table 2 Histological and immunohistochemical features of sinonasal leiomyosarcomas (n=9)

No.	Histology	Grade	SMA	Desmin	h-caldesmon	HMB45	S100	EBER ISH	Rb1	TP53	MDM2	CDK4
1	Conventional	G3	+++	+++	+++	–	–	–	Lost	–	–	–
2	Conventional low-grade	Initially G1; recurrence G2; Metastasis G3	+++	+++	+++	–	–	–	Lost	–	–	–
3	Conventional	G3	+	+++	+++	–	–	–	Lost	–	–	–
4	clear cell, glycogen-rich	G3	+++	++	+++	–	–	np	np	np	–	np
5	Conventional low-grade with dedifferentiation	G1 + G3	+++	–	–	–	–	–	Lost	–	–	–
6	Conventional	G3	+++	+++	–	–	–	–	Intact	+++	–	–
7	Conventional, focal myxoid	G2	+++	+++	+++	–	–	–	Lost	–	–	–
8	Conventional with clear cell and dedifferentiated (inflammatory MFH-like)	G1 + G3	+++	+++	+/–	–	–	–	Lost	–	–	–
9	Conventional, focal epithelioid	G3	+++	–	++	–	–	–	Intact	–	–	–

ISH in-situ hybridization, *np* not performed, *SMA* smooth muscle actin, *EBER ISH* Epstein Barr virus in-situ hybridization

Another interesting finding is the histological and immunophenotypic heterogeneity of SNT LMS with 2 cases showing focal dedifferentiation while 2 other cases showing glycogen-rich clear cell histology, mimicking perivascular epithelioid cell tumors (PEComas). However, unlike monotypic angiomyolipoma (PEComa) [11], none expressed the melanocytic markers. Instead, both tumors showed high-grade nuclear features consistent with leiomyosarcoma. From our data, dedifferentiation (observed in two tumors) does not seem to be associated with or explained by aberrant expression of TP53, MDM2 or CDK4. The frequent loss of nuclear RB1 in SNT LMS parallels their soft tissue counterparts and is not indicative of a genetic or heritable basis.

Distinguishing SNT LMS from benign smooth muscle tumors is usually straight forward given that the majority are high-grade tumors. Sinonasal leiomyoma (angioleiomyoma) is the second most commonly reported smooth muscle tumor at this site [12]. These usually small polypoid lesions are identical to their cutaneous counterparts and lack atypia and mitotic activity. A variable mature fatty component is observed in several lesions [12]. The latter feature is absent in SNT LMS. Likewise, thick-walled blood vessels are not a feature of SNT LMS, although a vascular smooth muscle origin has been proposed by some authors [5]. However, a rare subset of SNT LMSs shows intermediate features between benign leiomyoma (no mitoses) and leiomyosarcoma with brisk mitotic activity (defined as > 10 mitoses/10 high power fields). Analogous to soft tissue counterparts, the term smooth muscle tumor of unknown malignant potential has been used by some authors [5]. In our experience however, this variant of sinonasal smooth muscle tumors is exceptionally rare. We encountered none in our combined files. Likewise, SNT smooth muscle tumors with symplastic or bizarre nuclear features are exceptionally rare [13].

Spindle cell carcinoma, which can also occur in the post-radiation setting and may show some immunopositivity for smooth muscle markers, represents an important differential diagnosis of SNT LMS. While a subset of spindle cell SCCs are keratin negative, they lack histological features of smooth muscle differentiation (cigar-shaped blunt-ended nuclei, brightly eosinophilic cytoplasm, perinuclear halos/vacuoles and uniform fascicular growth pattern), are usually prominently polypoid, and when SMA is positive, it is usually only focal and weak. Most importantly, they are not desmin-positive, except those with rhabdomyoblastic differentiation, which are rare [14]. The presence of surface dysplasia or foci of carcinoma in situ are strong clues that aid in diagnosing spindle cell squamous cell carcinoma.

It is most important for therapeutic and prognostic reasons to recognize biphenotypic sinonasal sarcomas (BSS), which shows combined myoneural features and is separate from genuine LMS. BSS can be recognized on routine H&E stained material as a non-LMS given their basophilic
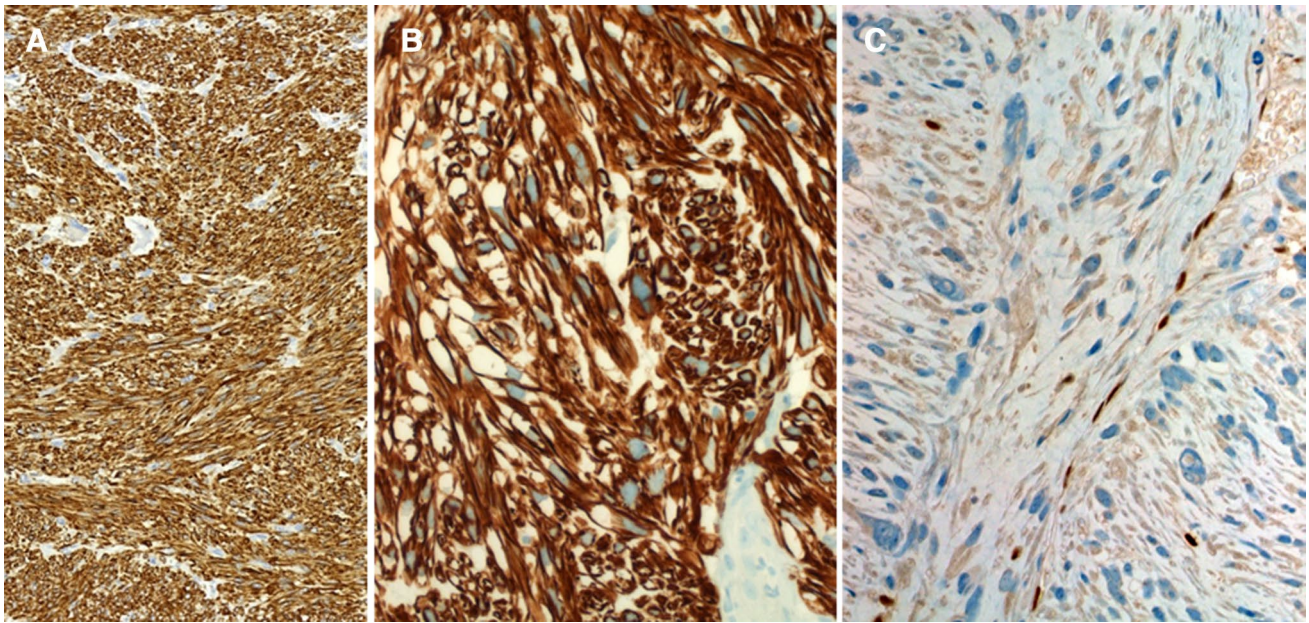
Fig. 3 Sinonasal leiomyosarcomas with strong expression of smooth muscle actin (**a**) and h-caldesmon (**b**). Loss of Rb1 (**c**) was observed in 6 of 8 tumors

(fibrosarcoma-like) morphology [15, 16]. However, IHC can be misleading as this rare and newly defined sarcoma type frequently expresses smooth muscle markers such as actins and less frequently desmin, thus suggesting a smooth muscle tumor if one is not aware of the entity or if other stains have not been concurrently performed (S100 protein and ß-catenin) [16]. In our series, none of the 9 LMSs expressed S100 protein, which is in contrast to the frequent co-expression of this marker in BSS. Furthermore, BSS is characterized by a distinctive gene fusion involving the MAML3 and PAX3 gene loci in majority of cases [17]. Indeed, inclusion of some BSS cases in older series/case reports of SNT LMS might explain the reported lower rate of distant metastases in the literature. EBV has been suggested as a possible etiologic agent for some smooth muscle tumors, especially in children and the immunocompromised [18], but we were not able to confirm EBV association (by EBER) in this series.

An important distinction, albeit rare, is to exclude sinonasal metastasis from LMS of other sites. We excluded from this study the one case of sinonasal metastasis from a LMS of the soft tissue of the hand. A few reports in the literature showed similarly rare metastases of uterine and soft tissue LMS to the head and neck area, including the sinonasal tract, suggesting a need for careful staging procedures to exclude another primary tumor [19, 20].

In summary, we herein described our experience with 9 sinonasal tract leiomyosarcomas highlighting their frequent, in part yet unexplained, association with previous cancer therapy and/or other synchronous/metachronous malignancies, their high propensity for local and occasionally fatal disease relapse, their high (50%) late distant metastatic rate, and occasional long survival irrespective of systemic metastasis, possibly as a result of improved multimodality therapy. These findings underscore the need for optimized therapeutic approaches and long-term follow-up with careful consideration of local therapeutic strategies for oligometastatic disease for each patient.

Compliance with Ethical Standards

Conflict of interest All authors declare that he/she has no conflict of interest as it relates to this research project.

Ethical Approval All procedures performed in this retrospective data analysis involving human participants were in accordance with the ethical standards of the institutional review board, which did not require informed consent.

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