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REVIEW ARTICLE

Inflammatory myofibroblastic tumors of the nasal cavity and paranasal sinus: a clinicopathologic study of 25 cases and review of the literature

Chun-yan He · Ge-hong Dong · Dong-mei Yang · Hong-gang Liu

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Abstract Inflammatory myofibroblastic tumor (IMT) is rare in nasal cavity and paranasal sinus. The aim of this study was to describe the clinicopathological features of sinonasal IMT and analyze the relationship between the clinicopathological features and the prognosis. A retrospective study of 25 IMT patients between 2001 and 2012 was performed. Data on clinical features, treatment, and follow-up were recorded. The histological characters were observed. Overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan–Meier method. Clinically, the most common symptoms were nasal obstruction, facial pain, and toothache. Twenty patients received follow-ups 6–120 months after initial diagnosis. Fifteen (75 %) developed recurrence 1 or more times. One patient had left cervical lymph node metastasis (5 %). Five patients died of the tumor (25 %). Histologically, the IMTs composed of bland spindle cells admixed with a prominent infiltrate of plasma cells and lymphocytes and showed obvious atypia in recurrent cases. Histology with necrosis, mitosis (≥1/10 HPF), ganglion-like cells, histological pattern I or II and relapse (≥4 times) was significantly associated with poor OS and EFS. IMT of the nasal cavity and paranasal sinuses exhibits relatively bland histologic appearances, but can shows strongly aggressive behavior and relatively poor outcomes. Multiple relapse, necrosis, frequent mitosis, the presence of ganglion-like cells, and histological pattern might be associated with poor clinical outcomes.

C. He · G. Dong · D. Yang · H. Liu (✉)
Department of Pathology, Beijing Tongren Hospital, Capital Medical University, No.1, Dongjiaominxiang, Street. Dongcheng District, Beijing 100730, China
e-mail: liuhg1125@163.com

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Introduction

Inflammatory myofibroblastic tumor (IMT) is a rather uncommon lesion. The World Health Organization classification currently defines IMT as an intermediate soft tissue tumor comprising spindle cells that exhibit myofibroblast differentiation and are accompanied by numerous inflammatory cells, plasma cells, and/or lymphocytes [1]. In most cases, IMTs behave as benign lesions, but invasive, locally recurrent, and metastatic forms of extrapulmonary IMT have also been reported [2–4]. The head and neck region is relatively less commonly involved [2–4]. To the best of our knowledge, only about 40 cases of IMT affecting the nasal cavity and paranasal sinuses have been previously reported in the English language literature. Most of these studies were case reports, and several showed more aggressive behavior and a fatal outcome compared with reports of IMT in other anatomic locations [2, 5–7]. However, there was no study exploring the prognostic factors of sinonasal IMT. We herein present a series of IMTs that originated in the nasal cavity and paranasal sinuses, describe the clinicopathological features and analyze the relationship between the clinicopathological features and the prognosis.

Methods and materials

The medical records associated with 25 cases of sinonasal IMT were obtained from the routine surgical files of the Department of Pathology, Beijing Tongren Hospital, Capital Medical University between 2001 and 2012. The

original slides of all patients were reviewed by two senior pathologists. The histological characters were observed and recorded. Clinical and follow-up information of the patients was obtained directly from the patients/patients' guardians and the medical records. Ethical approval was obtained from the Hospital Review Board.

Immunohistochemical staining

Immunohistochemical staining was performed on 4-μm thick unstained sections cut from representative formalin-fixed paraffin-embedded blocks by EnVision system with appropriate positive and negative controls. The antibodies used, dilutions and sources are shown in Table 1.

Statistical analysis was performed using SPSS 20.0 software package (SPSS, Chicago, IL). Overall survival (OS, defined as time from first surgery performed to death) and event-free survival (EFS, defined as time from first surgery performed to first relapse) were estimated using the Kaplan–Meier method. Univariate analysis involved location, age, gender, mitotic figures, necrosis, ganglion-like cells, Ki-67 index, immunohistochemical staining, histological pattern, and relapse. The cox regression was used to multivariate analyses. A p value of ≤ 0.05 was considered statistically significant.

Results

Clinical data

The clinical data of the 25 patients are summarized in Table 2. The age of patients ranged from 2 to 74 years (mean 41.2 years, median 42 years). 9 patients (36 %) were men, and 16 (64 %) were women; 2 were children, and 23 were adults. The tumors were located in the maxillary sinus ($n = 15$); maxillary sinus and nasal cavity, ethmoid sinus, or orbit simultaneously ($n = 6$); nasal cavity ($n = 1$); sphenoid sinus ($n = 1$); ethmoid sinus ($n = 1$); and orbit and frontal sinus ($n = 1$). Clinically, the most common symptom was nasal obstruction ($n = 9$), followed in turn by facial pain ($n = 8$), toothache ($n = 5$), headache ($n = 4$), head/face numbness ($n = 4$), facial swelling ($n = 4$), and decreased vision ($n = 4$). Uncommon symptoms included epiphora, eye swelling and pain, diplopia, epistaxis, and proptosis. Computed tomography (CT) and/or magnetic resonance imaging (MRI) revealed a soft tissue mass in the paranasal sinuses and nasal cavity with varying degrees of sinus wall erosion or bone resorption (Fig. 1). Eleven patients were treated with tumor excision by endoscopic surgery, seven patients with a Caldwell-Luc approach combining the endoscopic surgery, and seven patients received

Table 1 Antibodies used in this study

Antibody	Clone	Source	Dilution
vimentin	V9	Dako	1:100
SMA	1A4	Dako	1:100
MSA	HHF35	Dako	1:100
Calponin	EP63	Dako	1:100
Desmin	ZC18	Dako	1:100
Fibronectin	Polyclonal	Dako	1:300
ALK	ALK1	Dako	1:100
Cytokeratin	AE1/AE3	Dako	1:100
CD34	QBEnd/10	Dako	1:400
S-100	Polyclonal	Dako	1:100
Ki-67	MIB-1	Dako	1:100

SMA smooth muscle actin, *MSA* muscle-specific actin, *ALK* anaplastic lymphoma kinase

Nasal facial open surgery due the tumor involved multiple sites. Follow-up information was obtained for 20 patients (range 6 months–10 years); 15 patients (75 %) developed recurrence 1 or more times; 12 patients received 20–32 cycles (total dose 40–60 Gy) complementary radiotherapy (10 cases were recurrence); one patient received simultaneous complementary radiotherapy and chemotherapy; eight patients underwent maxillectomy, and one underwent right enucleation; one patient developed left cervical lymph node metastasis (5 %); five patients died of the tumor (25 %). After additional recurrences, most tumors involved multiple sinuses and extended into the nasal cavity or orbit or adjacent soft tissues. Seven cases involved the pterygopalatine fossa, of which four cases involved the infratemporal fossa and two cases involved the cavernous sinus. So far, four patients still survive with tumor.

Pathological and immunohistochemical findings

Grossly, most of the tumors were firm and fleshy with a white and tan cut surface. Hemorrhage and necrosis could be identified in recurrent cases. Histologically (summarized in Table 3), the IMTs was composed of fascicular spindle cells admixed with a prominent infiltrate of plasma cells, lymphocytes, and a few acute inflammatory cells in an edematous/myxoid stroma or collagenous stroma. The spindle cells were bland and had oval nuclei with small nucleoli and elongated cytoplasm. Three basic histological patterns were identified, consistent with those described by Coffin et al. [8]: myxoid/vascular pattern (I), compact spindle cell/cellular pattern (II), and hypocellular fibrous pattern (III). Patterns II and III were the predominating patterns in our patients (Fig. 2a–c). Tumor cells showed no cytological pleomorphism, atypia or necrosis and demonstrated low levels of nuclear mitotic activity

Table 2 Clinical characteristics

Gender			
Male			9 (36 %)
Female			16 (64 %)
Age			
Range			2–74 years
Mean			41.2 years
Median			44 years
Distribution			
<20			2 (8 %)
20–39	≥20	9 (36 %)	23 (92 %)
40–59		11 (44 %)	
≥60		3 (12 %)	
Subsites			
Maxillary			15 (60 %)
Maxillary and nasal cavity			3 (12 %)
Maxillary and other sites			3 (12 %)
Nasal cavity			1 (4 %)
Other sites (sphenoid, ethmoid, frontal sinus)			3 (12 %)
Clinical symptoms			
Nasal obstruction			9 (36 %)
Facial pain			8 (32 %)
Toothache			5 (20 %)
Headache			4 (16 %)
Head–face numbness			4 (16 %)
Facial swelling			4 (16 %)
Decreased vision			4 (16 %)
Epiphora			3 (12 %)
Eye swelling and pain			2 (8 %)
Diplopia			2 (8 %)
Epistaxis			2 (8 %)
Proptosis			2 (8 %)
Outcome of 20 cases (follow-up mean 3 years, median 2.5 years)			
No recurrence after last treatment			5 (25 %)
Recurrence			15 (75 %)
1 time			5 (25 %)
2–3 times			6 (30 %)
≥4 times			4 (20 %)
Metastasis			1 (5 %)
Death from disease			5 (25 %)

in the first resected specimens despite the fact that some tumors eroded the bone wall (Fig. 2d). Histological characteristics about high cellularity, nuclear atypia, mitosis, necrosis, ganglion-like cells, and high proliferation index were visible in part recurrent tumors (Fig. 2e–f), which were referred to as "malignant transformation". According to these criteria there were six recurrent tumors showing malignant transformation in our series.

Immunohistochemically (summarized in Table 3), the spindle cells were consistent with a myofibroblastic

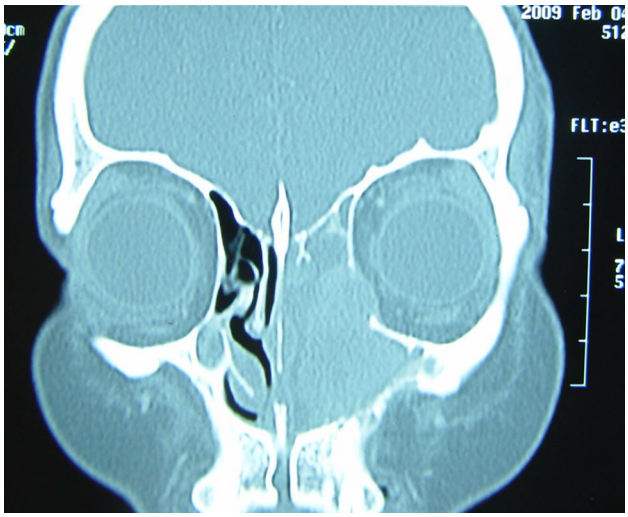

Fig. 1 CT showed a soft tissue mass filling the left nasal cavity and maxillary sinus. The mass had eroded the medial wall of the nose and the floor of the left orbit, and extended into the left orbit

phenotype. All 25 IMTs were diffusely positive for vimentin (Fig. 3a) and showed various positivity for alpha-smooth muscle actin (SMA). The positive staining of SMA was accentuated at the periphery of the cytoplasm, showing a linear staining pattern (Fig. 3b). More than half cases expressed with muscle-specific actin (Fig. 3c), fibronectin, calponin and a few cases were positive for Desmin, CK (AE1/AE3), S100 protein and CD34. One case (2-year-old boy) was positive for ALK-1.

Necrosis, high level of mitosis (≥1/10 HPF), the presence of ganglion-like cells, histological pattern (I or II), and relapse (≥4 times) were associated with poor clinical outcomes

Follow-up data were available for 20 patients, with the period after diagnosis ranging from 6 to 120 months (median 30 months). The 5-year OS was 80 %.

We performed a comprehensive analysis of the correlation between the clinicopathological parameters and the OS and EFS. The part results of the univariate analysis of prognostic variables are summarized in Table 4. Necrosis, a high level of mitosis (≥1/10 HPF), the presence of ganglion-like cells, and four or more relapses showed a significant association with poor OS ($p = 0.002$, 0.003, 0.007, and 0.012, respectively) (Fig. 4a). Necrosis, a high level of mitosis (≥1/10 HPF), the presence of ganglion-like cells, and histological pattern (I or II) showed a significant association with poor EFS ($p = 0.002$, 0.021, 0.009, and 0.044, respectively) (Fig. 4b). Multivariate analyses demonstrated that none of the clinicopathological parameters were independent prognostic markers.

Table 3 Histopathological and immunohistochemical characteristics

Histological pattern						
Pattern I						2 (8 %)
Pattern II						15 (60 %)
Pattern III						8 (32 %)
Histological characteristics						
Mitosis figure count (/10HPF)						
<1						17 (68 %)
1–5						4 (16 %)
≥5						4 (16 %)
With ganglion-like cells						7 (28 %)
Without ganglion-like cells						18 (72 %)
With necrosis						5 (20 %)
Without necrosis						20 (80 %)
Ki-67 index (%)						
<5						18 (62 %)
≥5						7 (28 %)
Malignant transformation						6 (24 %)
Immunohistochemical characteristics	−	+	2+	3+	4+	
Vimentin	0	0	2	5	18	25 (100 %)
SMA	0	5	3	8	9	25 (100 %)
MSA	10	9	2	4	0	15 (60 %)
Calponin	11	5	4	4	1	14 (56 %)
Desmin	23	0	1	0	1	2 (8 %)
Fibronectin	8	7	3	7	0	17 (68 %)
ALK1	24	0	0	1	0	1 (4 %)
CK	24	1	0	0	0	1 (4 %)
S100	21	2	2	0	0	4 (16 %)
CD34	24	0	1	0	0	1 (4 %)

−, negative; +, <10 % positive cells; 2+, 10–50 % positive cells; 3+, 50–75 % positive cells; 4+, >75 % positive cells; *SMA* smooth muscle actin, *MSA* muscle-specific actin, *ALK* anaplastic lymphoma kinase, *CK* cytokeratin

Discussion

IMT is described as a distinctive lesion composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate in the 2013 World Health Organization classification scheme [1]. It was separated from the broad category of non-neoplastic fibroinflammatory and neoplastic lesions referred to as inflammatory pseudotumor [4]. IMT occurs most commonly in the lung and abdomen, and can also arise anywhere in the body in patients of all ages. Extraorbital IMT of the head and neck region is relatively less common, accounting for about 5 % of all IMTs [3]. To the best of our knowledge, only about 40 cases of IMTs affecting the nasal cavity and paranasal sinuses have been previously reported in the English language literature.

According to our review of the literature (40 cases, 30 cases have follow-up records) [2, 6, 7, 9–23], sinonasal IMT can arise in patients of all ages (4–88 years; mean 39.3 years, median 40.5 years) and is more common in adults (70 %). In contrast, IMT in other anatomic locations tends to affect children and young adults. Women are slightly more commonly affected (62.5 %). Local symptoms include nasal obstruction, toothache, pain in the head and face, numbness, epistaxis, proptosis, blurred vision, and epiphora which are related to the site of origin. There are usually not systemic symptoms (e.g., anemia, unexplained fever, weight loss) or laboratory abnormalities. Sinonasal IMT is usually characterized by the simultaneous involvement of multiple sinuses and the nasal cavity. The most frequently affected site is the maxillary sinus, followed in turn by the nasal cavity, nasal septum, ethmoid sinus, and sphenoid sinus. CT or MRI shows a soft tissue mass in the involved sinuses and nasal cavity, and the mass is usually associated with destruction of at least one sinus wall. In the literature review, the tumors in four patients extended to the pterygopalatine fossa and infratemporal fossa, destroyed the orbital lateral wall or floor, and extended into the orbit in ten patients. The reviewed cases with follow-up records included recurrence in 9 patients (9/30, 30 %), distant metastases in 6 (6/30, 20 %), and death in 7 cases (7/30, 23.3 %). These rates are higher than the IMTs at other anatomic sites, which may be associated with the complex anatomy of the nasal cavity and sinuses [1, 4]. Children and young people under the age of

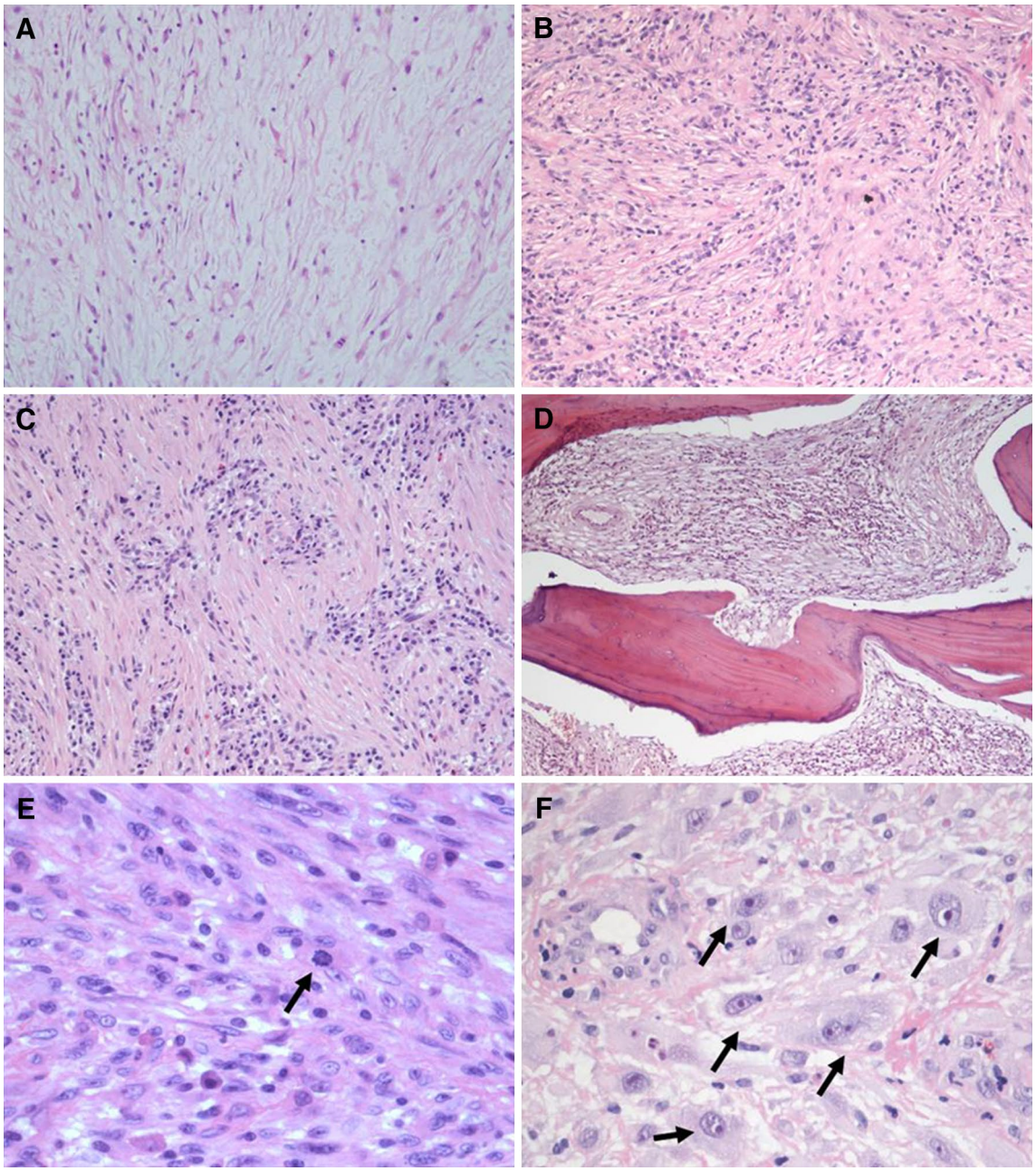

Fig. 2 IMTs (**a**) myxoid/vascular pattern. The tumor had an edematous, vascular background (HE, ×200). **b** Compact spindle cell pattern. The tumor had a fascicular architecture comprising dense proliferation of spindle cells admixed with plasma cells and lymphocytes (HE, ×200). **c** Hypocellular pattern. The tumor had relatively hypocellular with hyalinized stroma and plasma cells (HE, ×200). **d** The tumor eroded the bone wall (HE, ×100). **e** The recurrent tumor was a highly cellular with nuclear atypia and mitosis (*arrow*) (HE, ×400), and **f** ganglion-like cells (*arrows*) could be observed (HE, ×400)

18 years, however, had no recurrence, metastasis, or death. Our series showed similar clinical features (including gender, age, symptoms, laboratory findings and the locations) but a higher recurrence rate because there were only two patients under 18 years of age and one patient who developed three recurrences with eventual malignant change. Compared with sinonasal IMTs reported in the literature, our series showed a similar mortality rate but lower metastasis rate.

Histologically, IMT comprises myofibroblastic spindle cells admixed with a prominent infiltrate of lymphocytes, plasma cells, and acute inflammatory cells. Coffin et al. [8] described three basic histological patterns, which are often seen in combination within the same tumor: a myxoid/

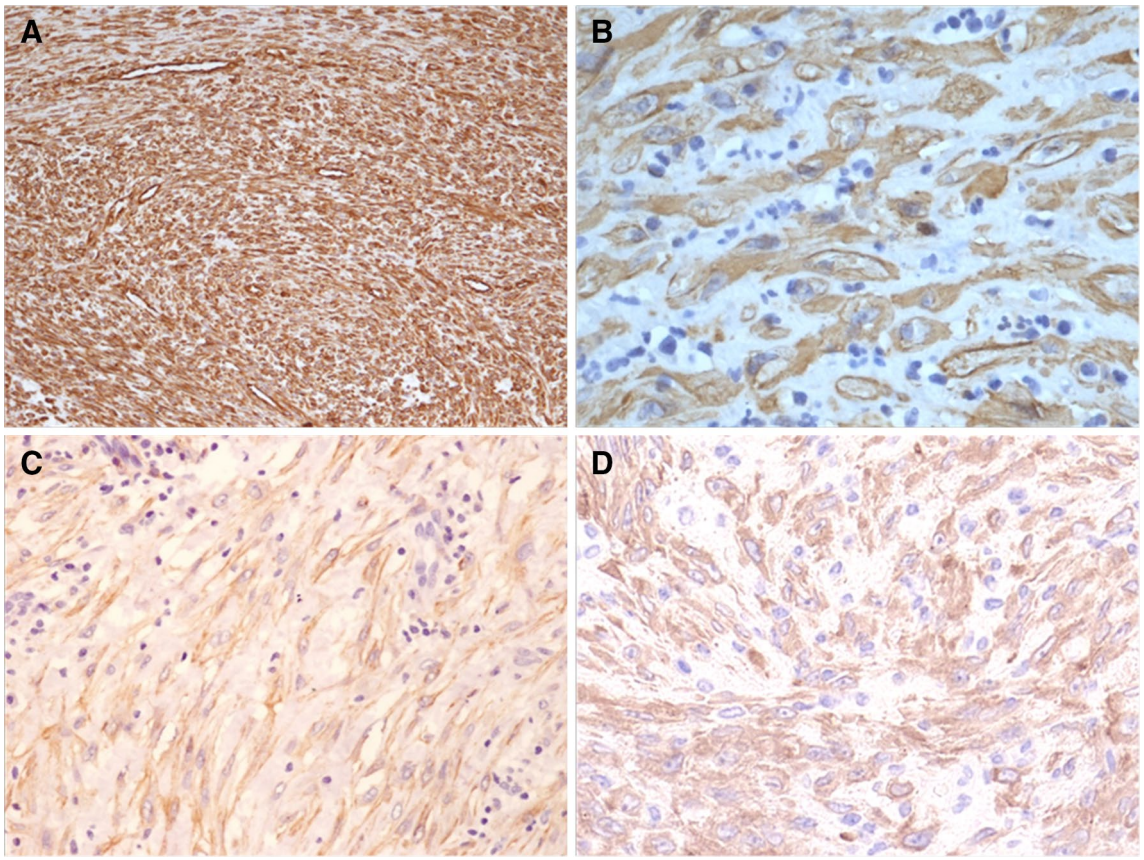

Fig. 3 Immunohistochemical staining. **a** The tumor cells were diffusely positive for vimentin. **b** The positive staining of SMA was accentuated at the periphery of the cytoplasm. **c** About half of the cases expressed MSA; most were mildly to moderately positive. **d** ALK-1 expression in a 2-year-old boy

vascular pattern, a compact spindle cell pattern, and a hypocellular fibrous (fibromatosis-like) pattern. Immunohistochemistry can confirm the myofibroblastic phenotype of the spindle cells, which are typically reactive to vimentin (99 %), SMA (92 %), MSA (89 %), desmin (69 %), and CK (36 %) [8]. The histological findings and vimentin and SMA staining results in our series of sinonasal IMTs were similar to those of IMTs in other locations. The positive rate of immunohistochemical staining of MSA, desmin, ALK-1 and CK was lower than that reported in the literature. This may be related to the low number of cases or different age distributions [4, 8]. Although there are no definite diagnostic criteria for malignant transformation, the combination of cellularity, cellular atypia, obvious nuclear mitosis, necrosis, ganglion-like cells and high proliferation index may imply malignant transformation [1, 4, 8].

Some studies have attempted to identify the histological predictors of aggressive behavior of IMTs and indicated that tumor size, cellularity, mitotic activity, and the presence of necrosis do not appear to correlate with outcome and nuclear atypia and ganglion-like cells might indicate more aggressive behavior [24, 25]. Few studies have reported the prognostic factors for sinonasal IMTs. Our study shows that necrosis, mitotic activity, ganglion-like cells, histological pattern (which may be associated with cellularity) and relapse were significantly associated with poor clinical outcomes in patients with sinonasal IMTs. These results in turn can illustrate above-mentioned malignant criteria as reasonable. There are no independent prognostic markers by multivariate analyses, may also be due to the low number of cases.

The differential diagnosis of sinonasal IMTs mainly includes lesions composed of myofibroblasts and fibroblasts. This may pose considerable challenges because of the morphological overlap of such lesions with IMTs. For example, low-grade myofibroblastic sarcoma (LGMS), inflammatory fibrosarcoma, nodular fasciitis, and diseases such as rhinoscleroma, Wegener's granulomatosis, and invasive fungal sinusitis can cause proliferation of myofibroblasts and fibroblasts. LGMS is considered to belong to the same family as IMT. The tumor cells are arranged in a herringbone-like pattern with obvious cellular atypia and nuclear mitosis, and the tumor displays invasive growth. Rare inflammatory cells are present within the tumor. It is

Table 4 Results of univariate analysis for prognosis evaluated by the Kaplan–Meier method

Factors		OS		EFS	
		5 years	*P**	5 years	*P**
Age (years)					
<59	$n = 18$	0.755	0.244	0.092	0.057
≥60	$n = 2$	0.500		0.000	
Gender					
Male	$n = 6$	0.417	0.125	0.333	0.245
Female	$n = 14$	0.825		0.094	
Site					
One site	$n = 15$	0.000	0.371	0.830	0.517
More than two sites	$n = 5$	0.200		0.600	
Necrosis					
Without necrosis	$n = 15$	0.900	**0.003**	0.116	**0.002**
With necrosis	$n = 5$	0.267		0.000	
Mitosis					
No or less than 1/10 HPF	$n = 12$	1.000	**0.007**	0.128	**0.021**
Equal to or more than 1/10 HPF	$n = 8$	0.365		0.000	
Ganglion-like cells					
Without ganglion-like cells	$n = 13$	1.000	**0.012**	0.147	**0.009**
With ganglion-like cells	$n = 7$	0.429		0.000	
Ki-67 index					
<5 %	$n = 13$	0.808	0.515	0.128	0.207
≥5 %	$n = 7$	0.000		0.000	
Histological pattern					
Pattern I or II	$n = 14$	0.627	0.169	0.000	**0.044**
Pattern III	$n = 6$			0.267	
Relapse					
No or 3 times	$n = 16$	0.938	**0.013**		
≥4 times	$n = 4$	0.250			

Bold values indicate statistically significant ($P \leq 0.05$)

OS overall survival, *EFS* event-free survival

* log-rank test

difficult to differentiate an LGMS from an IMT when the IMT has undergone malignant transformation. Inflammatory fibrosarcoma is considered to be an aggressive variant of IMT [26]. When myofibroblasts are set in a loose or myxoid stroma (myxoid/vascular pattern), the histological pattern may be indistinguishable from nodular fasciitis. However, IMTs are generally larger than nodular fasciitis and comprise short fascicular or storiform spindle cells in an inflammatory background rich in plasma cells. In contrast, nodular fasciitis usually lacks the striking inflammatory infiltrate characteristically present in IMT, demonstrates extravasation of erythrocytes, and is associated with a relatively short clinical course [2, 4, 8]. Rhinoscleroma usually contains foamy histiocytes (Mikulicz cells) in which bacilli (*Klebsiella rhinoscleromatis*) can be found with Warthin–Starry silver stain. Granulomatous vasculitis with fibrinoid necrosis is the main pathological changes in Wegener's granulomatosis. Other laboratory examination findings, such as abnormal antineutrophil cytoplasmic antibody results, support the diagnosis of Wegener's granulomatosis [4, 12]. The identification of fungal hyphae within the tissue allows for the diagnosis of invasive fungal sinusitis. Therefore, when diagnosing IMT, we must fully understand the history, examine the specimen thoroughly, and observe the sections carefully.

The etiology and pathogenesis of IMT remain unknown. Identification of chromosomal translocation of the *ALK* gene, which is located on chromosome 2p23, supports a neoplastic origin of IMT. Immunohistochemically, approximately 50 % of IMTs have been found to be positive for ALK (more commonly in younger patients) with reactivity ranging from 36 to 71 % [4, 27]. However, no ALK positivity has been described among all reported sinonasal IMTs. In our series, only one patient (a 2-year-old boy) showed immunoreactivity for ALK-1 protein. Accordingly, we believe that an *ALK* gene abnormality is not the major cause of adult sinonasal IMTs. Human herpesvirus 8 (HHV-8) and Epstein–Barr virus (EBV) DNA sequences have been described in adult pulmonary IMTs and in splenic and hepatic IMTs, respectively [28, 29], and a subset of IMTs is considered to be a type of IgG4-related disease [30]. However, there are no reports of HHV-8- or EBV-positivity or IgG4-related disease among sinonasal IMTs. Trauma and postinflammatory responses have been postulated as causes [31]. An association between trauma and IMT that may lead to reactive inflammation has been suggested, and three patients in our series had a history of facial trauma. However, such an association is difficult to establish in view of the scarcity of reported cases.

Because of the different clinical outcomes at different ages and sites, the treatment of IMT remains controversial [2, 7, 20]. In recent years, our otolaryngological surgeons noted the poor clinical outcome of sinonasal IMT. At present, the most commonly performed treatment is surgical excision of the tumor with a subsequent combination of radiotherapy, corticosteroids, and Chinese medicine adjuvant therapy. Radiotherapy was advised to patients (except children) at first surgery. When the tumor-recurred or tumor-involved adjacent structure or cellular atypia/invasive was described in the pathological report, all patients would be advised to receive radiotherapy regardless of adults or children. Chemotherapy would be advised to patients whose tumor recurred after surgery and radiotherapy or unsuccessful radiotherapy. Corticosteroids were routinely used for a short period before and after surgery. Some patients selected Chinese herbal treatment as an adjuvant therapy before and after surgery or radiotherapy to strengthen healthy and improve immunity. Although the

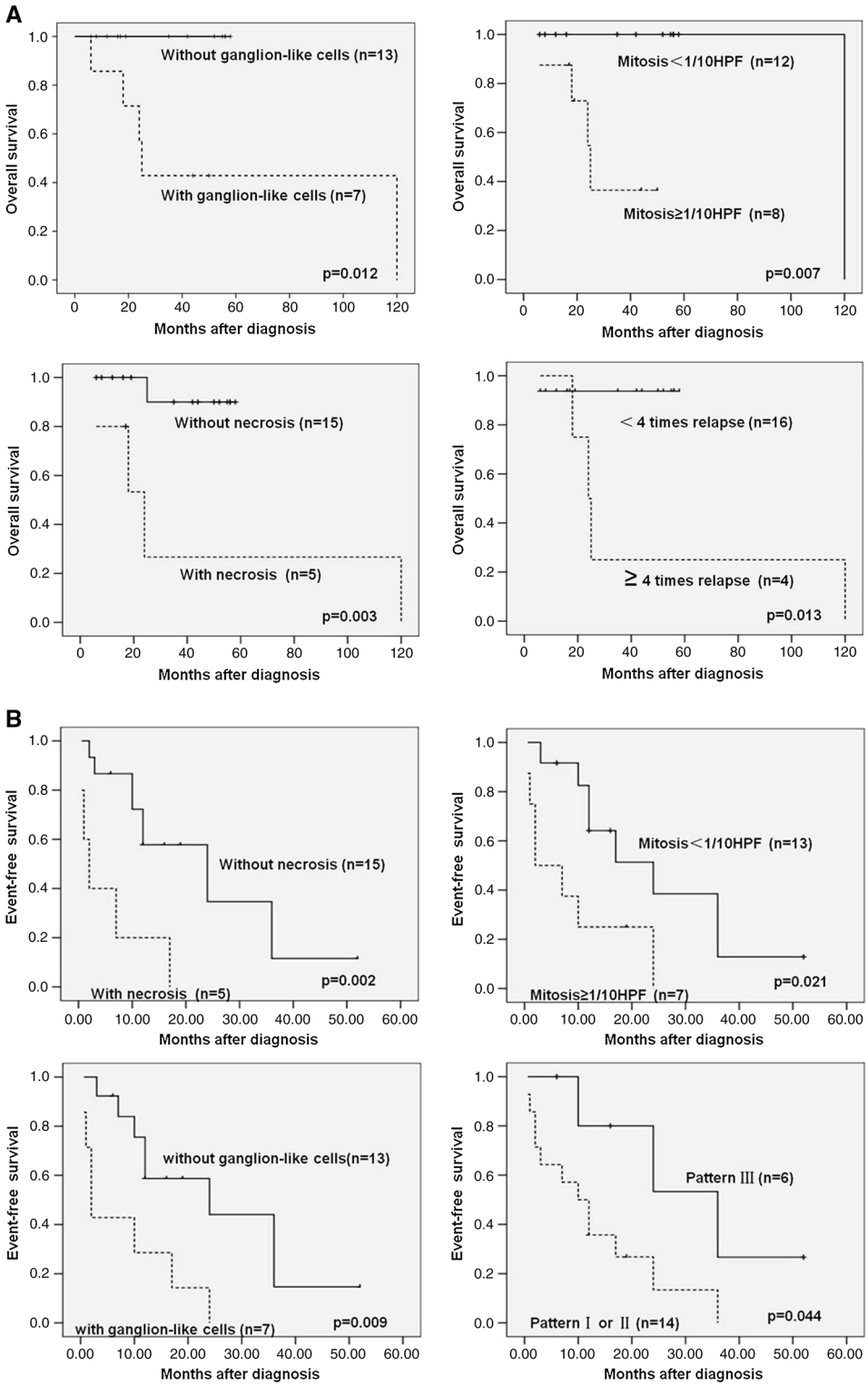

Fig. 4 **a** Necrosis, mitosis (≥1/10 HPF), the presence of ganglion-like cells, and relapses (≥4 times) showed a significant association with poor OS; **b** necrosis, mitosis (≥1/10 HPF), the presence of ganglion-like cells, and histological pattern I or II showed a significant association with poor EFS (*CT* computed tomography, *HE* hematoxylin and eosin, *SMA* smooth muscle actin, *MSA* muscle-specific actin, *ALK* anaplastic lymphoma kinase, *OS* overall survival, *EFS* event-free survial)

recent follow-up results were quite good, the long-term follow-up results are required to confirm the efficacy of this treatment.

In conclusion, although sinonasal IMTs exhibit relatively bland histologic appearances similar to those of their counterparts in other anatomic locations, they show more aggressive behavior and relatively poor outcomes. Necrosis, a high degree of mitosis (≥1/10 HPF), the presence of ganglion-like cells in histology, histological pattern I or II and relapse (≥4 times) were associated with poor clinical

outcomes. A prolonged postoperative follow-up period is necessary for patients with IMT.

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Conflict of interest The authors declare that they have no competing interests.

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